Proceedings

56th Annual Meeting of the Particle Therapy Cooperative Group (PTCOG)

8-13 May 2017

Hosted by the Kanagawa Cancer Center and the National Institute of Radiological Sciences, Japan

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Program Description

Overview

The main theme of this year's annual meeting is **Ion-beam Radiotherapy in the 21st Century: Accuracy and Efficacy**.

In recent years, the number of facilities dedicated to particle radiotherapy has been on the upswing throughout the world. Japan is no exception; today, five of the world's 10 carbon-ion radiotherapy facilities are in operation in the country. Since 1994, one of these, the National Institute of Radiological Sciences (NIRS), has conducted numerous clinical and research studies on the latest advances in the field.

On the first day of the conference, an expedition to NIRS to observe a rotating gantry using high-temperature superconducting magnets was offered. On the last day of the conference, attendees had the opportunity to tour the ion-beam Radiation Oncology Center in Kanagawa (i-ROCK), which specializes in a scanning irradiation method using 4 in-room computed tomography units.

Target Audience

- Physicians, Radiation Oncologists, Oncologists, Surgeons, Residents, and Fellows
- Medical Physicists, Dosimetrists, and Radiation Therapists
- Radiation Biologists, Accelerator Engineers, and Scientists
- Registered Nurses and Clinical Researchers
- Health Care Policy Makers, Insurance Executives, Industry Personnel, and Hospital Administrators

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Biomarkers and Models

PTC17-0400: Gene Signature to Predict Acute Toxicity in Carbon Ion Treated Prostate Cancer Patients

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Purpose: In the era of precision medicine, techonology-driven improvements including particle therapy and biology-driven advances have given radiation oncologists the capability to personalize treatments. Our hypothesis was that a molecular signature may serve as a predictive biomarker of carbon ion induced acute adverse effects.

Materials and Methods: From June to September 2014, 19 patients with T1c-T3a, histologically proven prostate cancer patients were enrolled. Patients received 63-66 GyE over 23-24 fractions. The primary end point was defined as the incidence of acute adverse events based on the CTCAE version 4.03. RNA-seq was performed using peripheral blood lymphocytes-derived RNA obtained at baseline. The series was split into training and testing cohorts. We performed boruta algorithm to identify feature genes related to carbon ion induced toxicity. Based on the selected gene sets, multiple classification model (support vector machines, random forests , k nearest neighbors , linear discriminant analysis, classification and regression trees) were applied for predicting a patient's likelihood of developing adverse effects.

Results: A set of 7 radiation-induced genes was identified capable of differentiating between patients with and without adverse effects. Predictive capabilities were obtained using different models for predicting new sample toxicity in training and testing sets. Based on the model evaluation, a 7-gene signature was established with two optimal classifiers(support vector machine and random forest).

Conclusion: A 7-gene signature has been identified as a useful new tool in predicting acute GI and GU toxicity. The classifying potential of the 7-gene signature has now to be validated in further patient cohorts.

PTC17-0309: Evaluation of a Model to Predict Post-Treatment MR Imaging Changes in Patients Treated for Brain Tumors with Proton Therapy

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The purpose of this study is to investigate the evaluative properties of a recently published model which describes the probability of the induction of post-treatment image changes as a function of dose and linear energy transfer (LET) in pediatric patients treated for brain tumors. The model was tested for other patients treated for brain tumors at our institution that were not included in the original study. For each patient, areas of post-treatment image change were identified on magnetic resonance imaging. Dose and LET distributions were calculated with Monte Carlo. The model was used to calculate receiver operating characteristic curves and corresponding areas under the curves (AUC) based on its predictions of image change compared to identified areas of post-treatment image changes. A volume-based histogram of the probability of image change values predicted by the model was also calculated for the region of image change, brain, and brain stem for each of the patients. The AUC values produced from testing the model on the new patients were high (in many cases > 0.9), which indicated that the model predictions agreed well with the identified regions of image change. The probability of image change volume-histograms provided a reasonable method of evaluating the model predictions in the image change regions as compared to the brain or brain stem volumes. Future work will aim to implement the model into the optimization of intensity modulated proton therapy plans so that it may eventually be used in the design of treatment plans.

PTC17-0304: Distinct Signatures of Cellular Response to Proton and Carbon Ion Versus X-Ray Therapy Revealed by Metabolomics and Genome-Wide Transcriptome Analysis

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Treatment of pediatric and adult cancers localized close to sensitive organs with proton and carbon ions, compared to conventional X-ray therapy, benefits from maximal energy deposition and minimal radiation to healthy adjacent tissue. Physical properties of X-ray, proton and carbon ions have been intensely compared and contrasted, but our understanding of the molecular and cellular responses to these radiation types remains in its infancy. Expanding this knowledge base is likely to create opportunities for improved radiation regimens and combinatorial treatments. Herein we take advantage of the research-dedicated gantry of the new Proton Therapy Center at Cincinnati Children's Hospital Medical Center (USA), in collaboration with the Heidelberg Ion-Beam Therapy Center (Germany), and compare OMICs responses of lymphoma and head and neck squamous cell carcinoma cells. The cells were subjected to X-ray, proton and carbon ion beam treatment at equal relative biological effectiveness as defined by colony formation and flow cytometric analysis of cell death. Cells were immunostained for γH2AX foci over time, as a measure of DNA damage and repair, and were globally profiled by RNA-sequencing. Cellular media was subjected to NMR metabolomics analysis. The results of these experiments highlight the existence of shared as well as radiation-specific cellular effects. Cell type and genetic background dependent transcriptional responses could be clearly defined. We identify the unfolded protein response (UPR) as a proton/carbon ion specific marker, and are currently exploring pharmacological and genetic UPR targeting for tumor cell sensitization as a possible novel adjuvant therapy.

PTC17-0295: Radiobiological Effects of Photon vs. Proton vs. Carbon Ion Irradiation on Human Pluripotent-Stem-Cell-Derived Gastro Intestinal Organoids

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Gastrointestinal (GI) toxicity constitutes an important obstacle in delivery of curative doses of radiotherapy. Advanced models recapitulating human GI physiology are urgently needed for a comprehensive radiobiological characterization of this radiosensitive organ. Towards this goal, generation of organ like structures termed "organoids" from pluripotent stem cells is an emerging technology for dissecting normal tissue response and toxicity in a tissue specific context. Human gastrointestinal organoids (HIO) can be derived from patient specific or genome edited pluripotent stem cells. We report here a systematic characterization of HIO for photon- and particle therapies (proton and carbon ion irradiation). Morphological, functional and molecular effects of the three radiation qualities was investigated by means of immunohistology and genome-wide transcriptional response (mRNA and microRNA). Irradiation induced DNA-double-strand-breaks were successfully detected in cryopreserved organoids by staining of 53BP1 foci enabling the analyses of DNA repair kinetics in different mature intestinal cell types present in HIO. Following unsupervised hierarchical clustering of gene expression signatures we selected for the strongest differences within the irradiated compared to non-irradiated HIO. In order to identify early- and late transcriptional changes in response to photon and particle therapy z-transformed expression values were compared 12 and 48 hours following irradiation. This comparison revealed that the strongest differences in gene expression detected in organoids are enriched in radiotherapy relevant pathways and distinguish radiation qualities as well as dynamics of early and late transcriptional changes following irradiation. Human pluripotent-stem-cell-derived organoids therefore provide an attractive model to study radiotherapy response and toxicity independent of animal models.

PTC17-0283: Dynamic Change of Phenotyping and Karyotyping of Circulating Tumor Cells in Prostate Cancer Treated with Carbon Ion Therapy

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Purpose: The purpose of this study is to evaluate the phenotyping and karyotyping of circulating tumor cells (CTCs) in prostate cancer patients treated with carbon ion radiotherapy (CIRT), in order to investigate circulating tumor cells heterogeneity during carbon ion therapy.

Materials and Methods: Subtraction enrichment combined with fluorescence in situ hybridization (FISH) and immunocytochemistry were used to detect and characterize of CTCs in prostate cancer and identification of aneuploidy CTCs. When patient's CTCs number more than 5, whole genome amplification were analyzed by NGS based on the different ploidies of chromosomes 8.

Results: A total of 65 patients with pathologically confirmed prostate cancer were treated with carbon ion therapy from May 2015 to Oct 2016. Blood samples were collected from part of the prostate cancer patients (n=39) pre- and post- carbon ion radiotherapy. CTCs could be detected in these patient population and following carbon ion therapy CTCs appeared to decrease. Further karyotypic analysis indicated that the ratio of tetraploid and multiploid CTCs were decreased after CIRT, but for triploid CTCs were increased after CIRT. We observed inter- and intra- patient heterogeneity in the mutation status of CTCs, we fund these mutations in multiploid CTCs were primarily associated with response to starvation, protein demethylation, and blood vessel development.

Conclusion: Our results investigated the phenotyping and karyotyping of CTCs had clinical potential for monitoring carbon ion therapeutic efficacy for prostate cancer.

PTC17-0246: Dose Absorption by Bystander Gold Nanoparticles Under Proton Irradiation

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Purpose: When gold nanoparticles (GNPs) form clusters inside a tumor cell, the distance between each GNP shrinks, which leads to the dose absorption by bystander GNPs. However, this dose absorption was not taken into account in previous calculations of dose enhancement. The purpose of this study is to investigate this effect in GNP cluster under proton irradiation.

Materials and Method: Monte Carlo simulations using Geant4 were conducted in two steps. First, GNP with diameters 2, 20, and 50 nm was bombarded with 10, 50, and 100 MeV protons from a disc source of the same diameter with the GNP. The energy distribution of electrons was calculated at the surface of the GNP. Second, the energy spectrum of electrons was used in another disc source to irradiate the bystander GNP. The distances to the bystander GNP (d) varied from 0 to 100 nm and the energy depositions by electrons to the surrounding water was evaluated.

Results: As the distance between GNPs increased, the dose absorption by the bystander GNP decreased with less electrons hitting the GNP. In the case of 10 MeV proton irradiation, about 13% of the dose was absorbed by the bystander GNP positioned in 20 nm away. Lower energy protons and larger GNPs showed higher dose absorption rate.

Conclusion: The dose absorption by the bystander GNP was influenced by the distance between GNPs, incident proton energy, and GNP diameter. The dose enhancement is overestimated if the dose absorption by the bystander GNPs is not taken into account.

PTC17-0231: Carbon Ion Therapy Affects the Expression of Plasma MicroRNAs of Prostate Cancer Patients Before vs. After Treatment

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Circulating microRNAs (miRNAs) hold great promise as novel clinically blood-based biomarkers for cancer. However, little is known about their impact in prostate cancer patients by carbon ion therapy. Our study aims to investigate the impact of carbon ion therapy on the expression of plasma microRNAs of prostate cancer patients by comparing pre- and post-treatment. The miRNA TLDA assay was performed as an initial survey to determine the serum miRNA expression profile from 19 localized prostate cancer patients. We selected 762 miRNAs, which were reported to be associated with carcinogenesis or radiobiology of prostate cancer, as the targets of miRNA TLDA assay in our study. The serum levels of miR-1247, miR-203, miR-302a, miR-342, miR-410, miR-492, miR-518f, miR-519c, miR-520e, and miR-595 were significantly increased, whereas the serum levels of miR-339 and miR-539 were markedly decreased after treatment than before treatment ($P < 0.05$). Furthermore, these changes in miRNAs expression are likely to be associated with the radiobiological effects of heavy ions. Further analysis will focus on assessing the association of changes in these miRNAs with the efficacy and toxic side effects of carbon ion radiotherapy. For the first time, our present study revealed changes in plasma miRNA after heavy ion therapy, which may have the potential to be used clinically as an auxiliary tool for carbon ion therapy for prostate cancer patients.

PTC17-0107: Improvement of Particle Therapy Protocols in Hypoxic Tumors Using Metallic Nanoparticles

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Low oxygen concentration in tumors results in lower cell death after exposure to radiation. The oxygen effect is expressed by the Oxygen Enhancement Ratio (OER) which depends, among others, on the oxygen level and the linear energy transfer (LET) of the radiation. Particle therapy benefits the treatment of hypoxic tumors compared to radiotherapy due to a decrease of OER when LET increases [Scifoni et al., 2013]. However, the irradiation of healthy tissues at the entrance channel remains a major limitation.

Nanotechnology brought new perspectives of using high-Z nanoparticles (NPs) to increase local radiation-effect. Previous studies performed by the group demonstrated that the radio-enhancement due to PtNPs is mostly related to the production of water radicals (OH) produced in the vicinity of the NPs [Porcel et al., 2010]. In parallel, it has been observed that the contribution of OH-mediated cell damage is strongly influenced by the presence of oxygen [Hirayama et al., 2013].

In the collaborative works performed at the Heavy Ion Medical Accelerator in Chiba (HIMAC, Japan) and at GSI-HIT (Germany), we investigated the effect of metallic NPs on human cancer cells incubated in oxic and hypoxic conditions and irradiated by carbon and helium ions. We have studied the variation of alpha and beta parameters in the presence of NPs. The presence of NPs might increase the direct lethal damage. This first study shows an attenuation of the amplification effect by NPs in the absence of oxygen. This gives new insights in the processes involved in the radio-enhancement by NPs.

PTC17-0020: The Effect of Mean Dose or Voxel-Wise Calculation in Prediction of Radiation-Induced Secondary Cancers

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Purpose: Increasing survival in cancer patients makes it important to study late side-effects, including radiation-induced secondary cancers. Although some predictive models exist, the accuracy of these models in radiotherapy dose range is limited partly due to data scarcity and partly by extrapolation beyond historical data bounds. One of the challenges when applying models to the highly spatially varying dose distributions produced in modern radiotherapy is dose heterogeneity within organs.This work investigates differences between using mean dose (MD) and high-resolution voxel-by-voxel dose (VbV) maps when modelling malignant induction probability (MIP).

Materials and Methods: 3DCRT and actively scanned proton plans were used for an adult and teenage patients with medulloblastoma. MIP is calculated using linear-quadratic (LQ), linear (LIN) and linear-no-threshold (LNT) models by an in-house developed code. MIPs calculated using the mean dose to the organs as well as VbV dose are compared for individual organs and the whole body.

Results: For the LNT model, the MD and VbV results are identical, as expected. For LQ and LIN, significant differences in MIP are seen. Organ-specific MIPs vary over a wide range, but MIPMD is higher than MIPVbV by an average factor of 2.2. Use of MD gives consistently higher MIP estimates than VbV in areas of dose heterogeneity.

Conclusion: Results demonstrate systematic differences between risk estimates produced using MD and VbV. Although the relative relation between MIPPhoton and MIPProton remains broadly constant, using MD in heterogeneous dose distributions potentially overestimates MIP and, by association, secondary cancer risk.

Relative Biological Effectiveness and Biological Optimization

PTC17-0509: Multi-Ion Simulations to Estimate RBE and Biological Dose Using the Microdosimetric Kinetic Model

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The PHITS Monte Carlo code paired with a microscopic analytical function was used to determine probability distribution functions of the lineal energy in 0.3μm diameter spheres throughout a water phantom. Pencil beams of 0.6cm diameter for ^{1}H, ^{4}He, ^{7}Li, ^{10}B, ^{12}C, ^{14}N, ^{16}O, and ^{20}Ne were simulated at energies that corresponded to physical Bragg peak depths of 50, 100, 150, 200, 250, and 300 mm. The acquired probability distribution functions were scored every millimeter transversely, and in annuli with outer radius of 1.0, 2.0, 3.0, 3.2, 3.4, 3.6, 4.0, 5.0, 10.0, 15.0, 20.0, and 25.0mm and then reduced to dose-mean lineal energies and applied to a modified microdosimetric kinetic model for five different cell types to calculate relative biological effectiveness (RBE) at the 10% survival threshold. The product of the calculated RBEs and the simulated physical dose was taken to create biological dose and comparisons were then made between the various ions.

For all beams the radial fluctuations in RBE were less then 4.2% while physical dose was greater than 1% of the maximum dose. Transversely, for the 50mm depth beams ^{7}Li was seen to provide the most optimal biological dose profile. For the other depth beams, ^{10}B was seen to provide the most optimal biological dose profile, followed by ^{12}C. The differences in these two beams reduced as initial energy was increased. Greater variance in cell-specific biological dose were seen for the more massive ions.

PTC17-0319: Proton Plan Robustness Evaluation and Re-Optimization Accounting for RBE Uncertainties

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Purpose: Incorporation of variable RBE and its uncertainties into proton plan robustness evaluation and re-optimization.

Materials and Methods: IMPT plans were generated for three breast, H&N and prostate patients. 2 Gy(RBE)/fraction in 25, 35 and 39 fractions were planned to each treatment site, respectively. 1.6 Gy(RBE)/fraction was prescribed to the low-risk H&N CTV. The dose was optimized assuming a constant RBE of 1.1. The plan robustness evaluation against setup and range uncertainties was performed assuming the constant RBE without uncertainties, and a variable RBE-model including uncertainties in model parameter, LET and α/β using a Monte Carlo method. Subsequently, the physical dose was re-optimized, such that the lower worst-case RBE-weighted dose to the CTV using the variable RBE-model agreed with the lower worst-case CTV dose in the original plan with RBE=1.1.

Results: All plans were considered robust when assuming the constant RBE, both in terms of CTV coverage and OAR doses. Applying the variable RBE-model shifts the nominal DVHs and broadens the error bounds for all structures studied. The uncertainty in α/β was found to be the dominant factor. The re-optimized plans showed similar lower worst-case CTV doses as the original plans using RBE=1.1, whereas the resulting OAR doses depended on treatment site.

Conclusions: Neglecting the variable RBE and its uncertainties might lead to underestimations of the variation in the RBE-weighted CTV and OAR doses. Accounting for this in a re-optimization of the physical dose may generate plans with satisfying worst-case CTV doses and acceptable OAR doses.

PTC17-0259: Influence of Unirradiated Volume to Irradiated Skin Damage After Carbon Ion Beams

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Purpose: Volume effects are long known for normal tissues including skin and central nervous system (CNS), and larger the irradiated volume severer the complication. Mechanisms underlying volume effect are almost unknown. Using mono peak of carbon ion beams, we irradiated mouse leg skin and studied whether unirradiated volume of leg affects to early skin reaction and late skin shrinkage of irradiated leg.

Materials and Methods: Hind legs of C3H/He female mice were irradiated with single doses of 135 MeV/u carbon ions. Irradiated leg was observed for skin reaction till Day 35, and also for skin shrinkage till Day 345.

Results: When outer leg skin received 12 Gy of 100 keV/micrometer carbon ions, skin score increased to 4.2. In case we added 24 Gy to inner skin, the peak score was higher than that of the outer-skin alone group even though this additional beam could not reach to outer skin. In 2nd experiments, dose responses of skin shrinkage were compared between 22 – and 100-keV/mm carbon ions. Maximum shrinkage after 22 keV/ micrometer carbon ions, which should have penetrated entire leg, was significantly higher than that after 100-keV/ micrometer carbon ions, which reached only 0.6 mm in leg.

Conclusions: Present data showed that irradiation to outer leg skin developed less skin reaction than irradiating an additional part of skin, i.e., inner skin. This means, at least, that response of irradiated skin is influenced by unirradiated skin. It is suggested that particle beams would be good to explore mechanisms underlying volume effects.

PTC17-0178: Targeting Cancer Stem Cells Using Carbon Ion Beam in Combination with DNA Damaging Drugs

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In this study, we try to explore the new molecular mechanisms of high radiocurability produced by carbon ion beam in combination with DNA damaging drugs (gemcitabine, 5-FU, cisplatin) s *in vitro* and *in vivo*. The colony, spheroid formation as well as tumorigenicity assays confirmed that subpopulation of CD44+/ESA+, and CD44+/CD24- cells exactly have cancer stem cell (CSC) properties in pancreatic and breast cancer cells. CSCs were more highly enriched after X-ray irradiation compared to carbon ion beam alone and in combination with gemcitabine, 5-FU or cisplatin extremely enhanced CSC proportion either by X-ray or carbon ion beam. The relative biological effectiveness (RBE) values for the carbon ion beam relative to X-ray at the D10 levels for CSCs were 2.1-2.4. The data showed that apoptosis- and autophagy-related gene expression was significantly induced after carbon ion beam combined with gemcitabine, 5-FU or cisplatin in pancreatic and breast cancer cells. We found that not only the number but also the size of γH2AX foci in CSCs were lager 24 h after carbon ion beam combined with gemcitabine, 5-FU or cisplatin compared to carbon ion beam and X-ray irradiation alone. *In vivo* study showed that 25 Gy of carbon ion beam combined with 50 mg/kg gemcitabine or 5mg/kg cisplatin effectively destroyed pancreatic and breast xenograft tumors. Taken together, carbon ion beam can achieve high curability when combined with DNA damaging drugs at relatively lower doses compared to carbon ion beam alone.

PTC17-0170: Characterization of Relative Biological Effectiveness (RBE) for Proton Therapy

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Purpose: Relative biological effectiveness (RBE) is utilized to account for the differences in biological effect from different radiation types. The RBE for proton therapy remains uncertain; it has been shown to vary from the clinically used value of 1.1.

Materials and Methods: Two cell lines were irradiated (CHO, Chinese hamster ovary; and A549, human lung adenocarcinoma) and assessed for cell survival using clonogenic assay. Cells were irradiated with 71 and 160 MeV protons and 6MV photons to various doses at depths along the Bragg curve. The dose averaged lineal energy (y_D), was measured under similar conditions as the cells using a microdosimeter. Dose averaged LET (LET_d) was also calculated using Monte Carlo simulations. Survival data were fit using the linear quadratic model. RBE values were calculated by comparing the physical dose (D6MV/Dp) that results in 50% (RBE_0.5), 10% (RBE_0.1) cell survival, and survival after 2Gy (RBE_2Gy).

Results: For 10% and 50% survival, the RBE for CHO and A549 cell lines increased with depth and were higher at 50% survival compared with 10% survival. The RBE at 2Gy also increased with depth in all cases, within experimental error.

Conclusion: Cellular response to radiation is varied and can be seen in the data from CHO and A549 cell lines irradiated with 71 MeV protons. A549 cells had higher RBE values, indicating a greater biological response to protons. The RBE values in this study vary from 1.03 – 2.31, indicating the clinical value of 1.1 may not be suitable in all cases.

PTC17-0141: Optimal Combined Proton-Photon Treatments in the Context of Fractionation

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Purpose: Proton treatment slots are a limited resource. We consider situations where most fractions are delivered with xrays and only a few with protons. We demonstrate how both modalities can be combined to optimally capitalize on the proton's ability to reduce normal tissue dose.

Materials and Methods: The problem relates to fractionation. We consider spinal metastasis treatments with epidural involvement. The target region abutting the spinal cord is best treated using uniform fractionation. Therefore, the xray fractions should be used. However, other parts of the target volume can be hypofractionated. In these areas, proton fractions can deliver higher doses than xray fractions, and thereby reduce normal tissue dose. Such combined treatments can be planned by simultaneously optimizing intensity-modulated proton and photon plans based on their cumulative biologically-effective dose (BED).

Results: The figure shows the dose distributions of an optimized proton-photon combination. The treatment consists of 4 xray fractions and one proton fraction. A BED of 60Gy(a/b=10), corresponding to 5x7Gy, is prescribed to the target. Near the spinal cord, the proton fraction delivers approximately the same dose as each xray fractions. However, in the remaining target volume, the proton fraction delivers, on average, twice the dose. Thereby, the single proton fraction realizes 50% of the normal tissue dose reduction that 5 proton fractions would yield (compared to 20% if both modalities deliver the same target dose).

Conclusion: A limited number of proton fractions can best be used if protons hypofractionate parts of the target volume. Such optimized proton-photon combinations substantially improve on naive combinations.

PTC17-0120: Charged Particle Combination Radio- and Immunotherapy

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Combination radiotherapy and immunotherapy is a topic of growing interest following promising clinical results. Ionizing radiation is immunogenic, inducing immunogenic cell death in tumor cells during treatment. This leads to immune activation, in turn potentially resulting in the shrinkage of metastases outside the irradiation field, a phenomenon termed the abscopal effect. Several clinical cases of the abscopal effect have been reported following radiotherapy, including with particle therapy. Charged particles, such as protons or carbon-ions, are thought to further increase the immunogenic effect. Immunotherapeutics, meanwhile, may boost immune response to extant disease and mitigate immunosuppressive signaling from tumor cells. The ultimate goal is to develop a combination treatment regimen using charged particles and a concomitant administration of immunotherapeutics, so as to reliably generate an abscopal effect. Under an international collaboration, NIRS/QST (Japan) and TIFPA (Italy) will conduct a comprehensive evaluation of combined particle irradiation and immunotherapeutic administration to assess the abscopal effect in mouse models. The abscopal tumor model is based on immune competent mice, such as C3H/He, which are injected with tumor cells in both hind limbs. The first limb-tumor simulates a primary, while the second simulates a distant metastasis; the first tumor is irradiated and immunotherapeutics are administered systemically, with changes in both tumors evaluated. Size change of the abscopal tumor is the primary endpoint, with quantitative and qualitative measures of the systemic immune response forming secondary endpoints. We will present preliminary results derived from this model.

PTC17-0099: Inhibition Effect of Metastasis by Carbon-Ion and Dendritic Cell Combined Therapy Depends on Host Genetic Background

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Purpose: Our previous research using an NR-S1-bearing C3H/He mouse model showed that carbon-ion (C-ion) and dendritic cells (DCs) combined therapy effectively inhibits distant lung metastases. Our aim is to investigate whether distant lung metastases can be inhibited by the C-ion and DCs combined therapy in other tumor-bearing mouse models.

Materials and Methods: 1) Mouse cancer cell lines (LM8, LLC, Colon-26 and Colon-26MGS) were grafted into hind leg of syngeneic mice (C3H/He, C57BL/6J, and BALB/c). Seven days later, tumors were irradiated with C-ions (290 MeV/n, 6-cm spread-out Bragg peak, 1 or 2 Gy). At 1.5 days after irradiation, immature DCs (iDCs) were administrated intravenously into mice. Lung metastasis was evaluated within three weeks after irradiation. 2) In vitro cultured cancer cells were irradiated with C-ions (290 MeV/n, mono-energy, 2 or 6 Gy), and then co-cultured with iDCs for three days to determine the maturation of DCs.

Results: Combined C-ion radiotherapy and iDCs immunotherapy effectively repressed distant lung metastases in a number of tumor (LM8 and LLC)-bearing mouse (C3H/He and C57BL/6J) models. On the other hand, colon carcinoma cells (Colon-26 and Colon-26MGS)-bearing BALB/c models did not show the enhancement of metastasis suppression by the combined treatment. An in vitro co-culture assay demonstrated that all irradiated cell lines were able to activate C3H/He- or C57BL/6J-derived iDCs into mature DCs, but not BALB/c-derived iDCs.

Conclusion: Our results reveal that the potency of combined therapy depends on the origin of the DCs governed by the genetic background of the host, and not on the type of cancer.

PTC17-0058: Impact of Variable Relative Biological Effectiveness in Treatment Plans of a Large Cohort of Intensity Modulated Proton Therapy Head-And-Neck Patients

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Purpose: We aim at evaluating the impact of variable RBE on Intensity Modulated Proton Therapy (IMPT) treatment plans of a large cohort Head-and-Neck (H&B) patients. The large cohort allows to evaluate the percentage of patients for whom differences are substantial. We are not aware of similar studies of this kind.

Materials and Methods: A cohort of 70 H&N patients, treated at the University of Texas Cancer Center with Intensity Modulated Proton Therapy (IMPT), were selected. H&N site was selected because of the highly inhomogeneous nature of the anatomy. A fast Monte Carlo (MC) code was utilized to recalculate the dose with fixed and variable RBE, with the Wilkens and McNamara models. The resulting estimates of the delivered dose distributions were compared to the original dose distributions calculated with the Treatment Planning System (TPS). DVHs, EUDs, and TCP and NTCPs computed using published models were utilized to evaluate the differences.

Results: MC results with fixed RBE predicts lower dose delivered in the target, with a EUD difference as large as 8 Gy. For variable RBE, the largest EUD differences are observed for the Larynx where 15% of the patients show an increase larger than 10 Gy.

Conclusion: Non-negligible differences between clinically used and variable RBE dose distributions are observed. Variable RBE dose distributions should be used as verification tools to avoid delivering unforeseen large doses to critical structures.

PTC17-0029: Proton Minibeam Sizes and Their Influence to Reduced Side Effects in an In-Vivo Mouse Ear Model

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Proton radiotherapy using minibeams of sub-millimeter dimensions reduces side effects of conventional proton therapy by spatial fractionation as shown in a first animal study (1). Tumor control is assumed to be maintained by homogeneous irradiation inside the tumor due to beam widening with depth. We report on the tissue sparing effect of partially widened proton minibeams as they occur on their way to the tumor within the healthy tissue. This comparative study uses six different minibeam sizes in the ear of Balb/c mice using 20MeV protons applied at the ion microprobe SNAKE (Munich). The average dose of 60 Gy is distributed in 4x4 minibeams, using Gaussian beam with sizes of σ=0.09, 0.2, 0.31, 0.45, 0.56, and 0.9 mm and beam-to-beam distance of 1.8 mm. Inflammatory response were measured by visible skin reactions and ear swelling and monitored for 90 days following irradiation. The biggest beam sizes lead to significant ear swelling, erythema and desquamation 3-4 weeks after irradiation. With decreasing beam sizes, the maximum skin reactions decreased until almost no ear swelling or other visible skin reactions could be found at any time after irradiation. These results demonstrate that proton minibeam radiotherapy has the best tissue sparing effect for the smallest beams. However, even quite large minibeams still show less acute side effects than a homogeneous dose distribution, as in conventional approaches, and suggest, that a proton minibeam radiotherapy reduces side effects to quite large depths and has the potential to become a new approach in clinical proton and/or heavy ion therapy. (1) Girst et al.,IJROBP 2016;95(1),234-241

PTC17-0019: Proton Minibeam Radiation Therapy Spares Normal Rat Brain

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Purpose: Proton minibeam radiation therapy (pMBRT) [1] is a novel concept allying the physical advantages of protons with the normal tissue preservation observed in minibeam radiation therapy [2]. We have recently implemented the technique [3] at the Orsay Proton therapy center. The main objective of this work was to confirm the gain in tissue sparing thanks to pMBRT.

Materials and Methods: Whole brains of 7 week-old male Fischer 344 rats (n=16) were irradiated with 100 MeV protons. Half of the animals received conventional seamless proton irradiation (25 Gy in one fraction). The other rats were irradiated with pMBRT (58 Gy peak dose in one fraction). The animals were observed for 7 months. A magnetic resonance imaging (MRI) follow up at a 7T small animal MRI scanner as well as histological analysis were performed.

Results: Rats treated with conventional proton irradiation exhibited severe moist desquamation, permanent epilation and important brain damage. In contrast, the pMBRT group presented neither skin damage nor significant brain damage.

Conclusion: pMBRT leads to an increase in normal tissue resistance. This gain in normal tissue sparing ccan open the door to an efficient treatment of very radioresistant tumors, which are currently mostly treated palliatively.

References: (1) Prezado et al. Med. Phys. 40, 031712, 1–8 (2013). (2) Prezado et al., Rad. Research. 184, 314-21 (2015). (3) Peucelle et al., Med. Phys. 42 7108-13 (2015).

PTC17-0018: Reducing Heart Toxicity in Medulloblastoma Using Proton Therapy

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Purpose: Radiotherapy is known to cause acute and long term side effects. Some side effects are a major reason of mortality in cancer survivors. Heart disease after radiotherapy for Hodgkin and breast cancer patients is a major cause for mortality that it is offsetting the benefits of treatment (EBCTCG, 2016). In this work, potential benefits of using proton therapy in treatment of medulloblastoma (MB) to reduce heart toxicity is discussed and compared with benefit gained in reduction of secondary cancer (SC).

Materials and Methods: Increase in risk for rate of major coronary events for 3DCRT and proton plans for patients with MB was calculated using published model (Darby et al,2014), the NTCP for cardiac perfusion deficits was modelled using LKB model (Das et al, 2005), and the mortality risk from ischemic heart disease (IHD) was modelled using relative seriality model (Kallman et al,1992, Eriksson et al,2000). Risk of mortality from SC was modelled as well using voxel-by-voxel dose maps and models that includes cell-kill components, linear quadratic (LQ) and linear model (LIN) (Timlin et al,2015).

Results: The heart mean dose for the patients are 16.1 & 20.38 Gy (3DCRT), and 0.1 and 0.03 Gy (Protons). Results are in tables 1 & 2.

Conclusion: Proton therapy for MB is expected to decreases risk of major cardiac events, mortality due to IHD and mortality from RT-induced secondary cancer significantly, compared to 3DCRT. With cardiac late side effects being a major clinical burden post-RT, arguably more than secondary cancer risk, these results strengthen the argument to use proton therapy.

Central Nervous System and Skull Base

PTC17-0526: Outcomes in Patients with Cervical Spine Chordoma Treated with a Combined Surgical and High-Dose Photon/Proton Beam Radiotherapy Approach

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Purpose: Cervical spine chordoma is often treated with combination surgical resection and radiotherapy.We report the outcomes in the largest series of cervical spine chordoma treated with surgery combined with high-dose photon/proton beam radiotherapy.

Materials and Methods: Retrospective analysis was performed on 109 patients with cervical spine chordoma treated during 1984-2014 at our institution.CTCAE version 4.0 was used to grade late treatment toxicity.

Results: Median age at diagnosis:51 years old (range:10-83). 86 (79%) and 11(10%) patients underwent surgery followed by radiotherapy or pre- and post-operative radiotherapy with surgery, respectively. 12 patients (11%) underwent surgery alone, radiotherapy alone or neither.82 patients (75%) had known margin status of which 7% and 63% had microscopic and gross positive margin, respectively. Surgical details were available in 74% of patients who underwent surgery, including transoral (19%), anterior (49%), posterior (41%) or transverse (32%) approach. 22% of patients underwent $>$1 surgical or a planned two-staged surgical approach. Spinal stabilization was performed in 60% of patients, including cervical (67%) or occipital (33%) approach. Median radiotherapy dose:75.2 GyRBE (range:48.6-83.2 GyRBE). Of 100 patients who received radiotherapy, 74% received combined photon/proton beam radiotherapy. Five-year LC, OS and MFS was 69.4% (95% CI:58.5-80.3%), 77.7% (95% CI:66.8-88.6%) and 93.6% (95% CI:87-100%), respectively. Late grade 3+ toxicity occurred in 16% of patients, including one grade 5 toxicity (recurrent chordoma at presentation, peri-operative mortality).

Conclusion: Treatment of cervical spine chordoma through combined surgical resection and high-dose photon/proton beam radiotherapy provides promising LC with acceptable rates of grade 3+ late toxicity. Longer follow-up is needed to interpret overall outcomes and toxicity.

PTC17-0517: Preliminary Results of a Choroidal Hemangiomas (CH) Series Treated by a Proton Therapy with a New Fractionation Schedule

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Purpose: Our late series of pts with CH treated with proton therapy, 20GyEBR with 4 fractions of 5GyEBR had showed 8% of late macula toxicities. Since 01/2010 CH have been treated with a new protocol 20GyEBR with 8 fractions of 2.5GyEBR to try to reduce late toxicity.

Results: Between 01/2010 and 04/2015, 45 pts had been treated. Before irradiation, all pts showed a reduction of their visual acuity score in relation with an exudative decompensation of the CH. 41 pts (91%) had a retinal detachment (RD).

The median follow-up was 20.5 months (7–62). One patient was lost during his follow up. At the last control, 44 pts (98%) had a regression of the hemangioma mass and 23pts (51%) had a completely flat scar. The retina was flat for all patients, except one for whom a small persistent RD was seen at 9-month. Visual acuity were improved or stabilized in 43 patients (96%) with a mean visual acuity score of 20/35. No early or late toxicity was detected.

Conclusion: The irradiation of the exudative circumscribed choroidal hemangiomas by proton with 20 GyEBR delivered in 8 fractions of 2,5GyEBR gave excellent results on the tumor thickness regression and the disappearance of the exudative phenomena. These results were similar to those obtained with 20GyEBR in 4 fractions of 5GyEBR. Follow-up of this series continues to determine whether long-term complications are avoided.

PTC17-0480: Proton Beam Therapy for Periorbital Skin Malignancies with Orbital Invasion

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Purpose: For patients with periorbital skin malignancies with involvement of the orbits, orbit exenteration is the standard of care. Proton beam allows excellent target coverage with maximal sparing of adjacent normal tissues. We evaluated the treatment outcome and toxicty in patients with periorbital skin malignancies with orbital invasion treated with proton beam therapy.

Materials and Methods: Between 2006 and 2015, 15 patients with periorbital skin malignancies received proton beam therapy at our institution to a median dose of 66.3Gy(RBE). The median age was 75. Sixty-nine percent of patients had recurrent tumors after resections. The histology subtypes were: basal cell carcinoma 56%, squamous cell carcinoma 25%, sebaceous cell carcinoma 13%, melanoma 6%. Fifty percent and 37% and of the lesions located in the medial/lateral canthus and upper/lower eyelids, respectively. Locoregional control probability was estimated with the Kaplan-Meier method. Treatment toxicity was scored using the CTCAE 4.0.

Results: The mean doses to the ipsilateral avoidance structures in Gy(RBE) were: optic nerve 0.6, optic chiasm 0, lens 5.5, , retina 17, lacrimal 1.4, cornea 11.9, brain 0.24. At a median follow up of 22 months, there was no local recurrence after proton beam therapy. The rate of orbital preservation rate was 100%. Acute toxicity was very limited with one grade 3 epiphora. One patient developed late grade 3 retinopathy. There was no acute or late grade $\geq$4 toxicity.

Conclusion: Proton therapy for periorbital skin cancer results in excellent local control with minimal acute and late toxicity.

PTC17-0453: Edema Extent of Glioblastoma Determined the Survival and Progression Pattern After Concurrent Chemoradiotherapy with Proton Beam

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Purpose: The preoperative edema (PE) extent of glioblastomas is highly associated with prognosis and progression patterns. We investigated the associations between the PE extent and outcomes after concurrent chemoradiotherapy (CCRT) with proton beam (PB).

Materials and Methods: The radiotherapy regimens comprised 50.4 Gy in 28 fractions delivered to edema plus 15 mm margin, followed by an additional concomitant boost of 23.1 GyE in 14 fractions with PB to contrast-enhanced tumors plus 10 mm margin at intervals more than 6 hours, and then 23.1 GyE in 14 fractions to contrast-enhanced tumors. The combined chemotherapy included either nimustine hydrochloride (ACNU) or temozolomide (TMZ). The extensive PE (EPE) and extensive progressive disease (EPD) were defined as PE and progressive tumor extending along PE with the distance from the tumor margin $>$18 mm, respectively.

Results: In total, 46 patients were followed for a median of 77.9 (range 30.0–125.7) months. The median overall survival (OS) for patients with EPE and without EPE were 18.2 versus 42.4 months ($p = 0.023$). Using multivariate analyses with the factors of age, performance, tumor size, and chemotherapy regimens (TMZ or ACNU), EPE remained significant for a poor OS (hazard ratio, 2.61 with 95% confidence interval, 1.11–6.15) (table 1). The EPD rate for tumors with and without EPE were 7.4% versus 40.6% ($p = 0.038$).

Conclusion: EPE of glioblastomas determined the survival and progression patterns after CCRT with PB. Compared with patients with EPE, the better OS and lower EPD rate suggest PB irradiation is indicated for those without EPE.

PTC17-0409: Comparison of Radiation Necrosis in Adult Cranial Gliomas Treated with Proton vs. Photon Therapy

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Purpose: Proton therapy is an emerging treatment modality for gliomas, but data on late effects are limited. We compared the incidence of and risk factors for clinically significant radiation necrosis (cRN) in adult cranial gliomas treated with proton vs. photon therapy.

Materials and Methods: Between 2007 and 2015, 160 adult patients with grade II/III glioma were treated with proton (n=37) or photon (n=123) with or without concurrent/sequential chemotherapy. cRN was defined as symptomatic RN or asymptomatic RN that resulted in surgery or bevacizumab treatment. cRN was ascertained based on all available clinical data and confirmed by a panel of 3 radiation oncologists blinded from treatment information. Cumulative incidence was calculated using competing risks. Risk factors were identified using Cox proportional hazards.

Results: Median follow up was 28.5 months. Median prescription dose was 5940cGy (5040-6300cGy). Eighteen patients developed cRN (proton=6, photon=12). Median time to cRN was 11 months (2.8–34.2 months). There was no significant difference in two-year cumulative incidence of cRN between proton vs. photon (18.7 vs. 9.7%; 95% Confidence Interval [CI]:7.5-33.8% vs. 5.1-16%; p=0.16). Proton was not a significant risk factor for cRN as compared to photon (Hazard Ratio [HR]:1.81, 95% CI:0.67–4.9, p=0.24). On multivariate analysis, only histology of 1p19q-codeleted oligodendroglioma was a significant risk factor for cRN (HR:3.13, 95% CI:1.21–8.1, p=0.02).

Conclusion: At 2 years, proton therapy has a modest incidence of cRN but not significantly different from photon therapy. Oligodendroglioma histology appears to be a significant risk factor for cRN.

PTC17-0150: PTCOG Consensus Statement on the Management of Conjunctival Melanomas

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Purpose: Rhere is a lack of consensus regarding it classification and management of conjunctival melanoma. We built an international Delphi-based consensus approach within the PTCOG community and related ophthalmologists/physicists.

Material and Methods: The iterative process first provided a wide range of opinions from a group of 12 experts (12 teams). The results of the first round of questions provided the basis from the second round of 101 questions, scored from 1 for no agreement to 9 for full agreement, presented here.

Results: Experts advocated against TEP-CT at diagnosis and during follow-up. Experts agreed on oncosurgery rules for the primary, on histology including integration of the recent CMIN classification and more systematic of biomarkers (BRAF, immune markers etc). They agreed on the use of brachytherapy plaques, with PT as an option. They agreed on adjuvant irradiation for invasive/microinvasive melanomas, exclusive irradiation as an option for diffuse melanomas, and mitomycine after irradiation in case of primary acquired melanosis (PAM). They advocated against clip placement, use of compensators, and irradiation in 4 fractions only during PT. They agreed against prophylactic irradiation (including thickness$>$0,2mm) for the clinically negative neck. Areas of controversy were surgery under local anethesia, sentinel node biopsy, nodal target volumes for node-positive melanomas, use of external beam photons/electrons irradiation, PT in case of corneal or eyelid involvement, irradiation of PAM, optimal PT planning/dosage/target volumes and strategies to increase local control.

Conclusion: Results from the second round of questions will feed into a third and final round before PTCOG.

PTC17-0065: Advancement in Craniospinal Irradiation with Use of Proton Pencil Beam Scanning: Benefits in Conformality, Complexity, and Cost

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The use of passively-scattered proton (PS) fields for craniospinal irradiation (CSI) has been shown to be advantageous over conventional photon therapy due to the lack of exit dose. PS offers great lens sparing through the use of aperture edges, but lacks skin dose sparing and requires cumbersome/expensive mutli-field feathering techniques.

Our institution now offers multiple dosimetric approaches for CSI treatment using proton pencil beam scanning (PBS). These approaches offer various degrees of lens sparing, skin sparing, gradual robust feathering, and modulated dosimetry with fewer fields than PS techniques, only limited by the clinical machine characteristics (maximum field size of 32 cm and spot size of 8 to 14 mm as a function of energy). For patients with favorable anatomy, as defined by adequate spacing between lenses and cribriform plate, and lower dose prescriptions, which enables better skin sparing, a simple PA-field technique with no aperture may be used.

In such cases, aggressive lens sparing can be achieved in order to protect against range uncertainties. For younger pediatric patients and/or 36+ GyRBE prescriptions, oblique fields with apertures may be used for the cranial field component to optimize lens and skin sparing, with the tradeoff of increased delivery practicality and cost. With PBS, gradual feathering is achieved with overlapping fields, resulting in highly robust treatment delivery. PBS can further be used to provide bone-marrow sparing to lessen the negative impact on growth for pediatric patients and marrow for all patients.

PTC17-0038: Proton Beam Therapy for Bone Sarcomas of the Skull Base and Spine: A Retrospective Nationwide Multicenter Study in Japan

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Purpose: Only a limited number of studies concerning the effectiveness of proton beam therapy (PBT) for bone sarcomas (BSs) of the skull base (SB) and spine have been published in Japan. We conducted a retrospective, nationwide, multicenter study to evaluate the clinical outcomes of PBT for BSs of the SB and spine in Japan.

Materials and Methods: Eligibility criteria included histologically proven BS of the SB or spine, no metastasis, $\geq$20 years of age, and no previous radiotherapy. Of the 103 patients treated between January 2004 and January 2012, we retrospectively analyzed data from 96 patients who were followed-up for $>$6 months or had died within 6 months.

Results: Seventy-two patients had chordoma, 20 patients had chondrosarcoma, and 4 patients had osteosarcoma. The most frequent tumor locations included the SB in 68 patients and the sacral spine in 13 patients. Patients received a median total dose of 70 Gy (relative biological effectiveness [RBE]) (biologically effective dose, alpha/beta = 10 Gy, 86 Gy [RBE]). The median follow-up was 52.6 (range, 6.3–131.9) months. The 5-year overall survival (OS), progression-free survival (PFS), and local control (LC) rates were 75.3%, 49.6%, and 71.1%, respectively. Performance status was a significant factor for OS and PFS, and sex was a significant factor for LC. Acute Grade 3 and late toxicities of $\geq$Grade 3 occurred in 9 patients each.

Conclusion: PBT is safe and effective for the treatment of BSs of the SB and spine in Japan. Larger prospective studies with a longer follow-up are warranted.

PTC17-0032: Outcomes of Patients with Iris Melanomas Treated with Proton Therapy

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Purpose: Proton therapy is a standard conservative treatment for choroidal melanomas. Iris melanomas are rare. Practice patterns and outcomes following PT were examined.

Material and Methods: a retrospective study of all consecutive patients referred from 3 ophthalmology centers (L, I, N) and treated at the same PT center (52Gy/4 fractions) between 1997 and 2014 was performed. Tumors having their epicenter in the ciliary body on ultrasound (US)/ ultrabiomicroscopy (UBM) were excluded.

Results: Of 107 patients, mean age was 57 yo, diameter 4,3mm (0.8-12.9), thickness 1.75 (0.5-5.6mm) and stage was T1, T2 or T3 in 66.0%, 22.9% or 11.1% of cases. Tumors were histology/cytology-proven in 10.3%, located inferiorly in 79.4%. The trabeculum or ciliary body was involved in 50.8% and 21.5% of cases. Cataract or ocular hypertension (OHT) was present at baseline in 27.7% or 16.9%.

Median follow-up was 4.1 years, crude local control was 95,3%. Five patients had a local relapse within a median time of 30 months. Two teams (L, I) had their patients in mydriasis during PT. Mydriasis during PT was associated with fewer rates of PT-induced cataract. De novo cataract, OHT or neovascular glaucoma was reported in 58.1%, 9.1% or 3.1% of patients. No patient was enucleated. Team I recommended inclusion of pigmented deposits in the target volume, no correlation with relapse could be drawn due to so few relapses. Specific survival was 100% with one patient having metastases at last follow-up.

Conclusion: Iris melanomas have distinct outcomes compared to choroidal melanomas. Proton therapy can be recommended.

Clinical Trials

PTC17-0300: Minimal Toxicity After Proton Beam Therapy for Prostate and Pelvic Nodal Irradiation: Results from the Proton Collaborative Group REG001-09 Trial

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Purpose: Proton therapy (PBT) reduces normal organ dose compared to intensity modulated radiation therapy (IMRT) for prostate cancer (PCa) patients who receive pelvic lymph node radiation (PLNR). It is not well described whether this dosimetric advantage results in less gastrointestinal (GI) and genitourinary (GU) toxicity than would be expected from IMRT.

Materials and Methods: We evaluated treatment parameters and toxicity outcomes for non-metastatic PCa patients who received PLNR and enrolled on the Proton Collaborative Group REG001-09 trial (NCT01255748). Patients who received photon therapy and/or brachytherapy were excluded.

Results: Of 3,210 total PCa patients, 85 received PLNR across 7 institutions from 2010-2016. Most were T2/3 and all were node-negative. Median Gleason score was 8 (range 6-10). Pre-PBT PSA was 8.21 ng/mL (0.1-126.18) although 60% started hormone therapy before PT. Median pelvic dose was 46.9 GyE (range 39.7-56) in 25 fractions (range 24-30). Median boost dose to the prostate +/- seminal vesicles was 30 GyE (range 20-41.4) in 16 fractions (range 10-24). Nearly 70% received pencil beam scanning. Median followup was 9.1 months (range 0.4-49.2). Acute and late grade 1, 2, and 3 GI toxicity rates were 16.4, 2.4, 0%, and 3.5, 2.4, and 1.2%, respectively. Acute and late grade 1, 2, and 3 GU toxicity rates were 60, 34.1, 0%, and 14.1, 3.5, and 0%, respectively.

Conclusion: PCa patients who receive PLNR using PBT experience significantly less GU, and especially GI, toxicity than is expected from IMRT likely due to significant sparing of small bowel, rectum, and bladder from low-to-intermediate dose.

PTC17-0268: Clinical Outcomes of Patients with Recurrent Lung Cancer Reirradiated with Proton Therapy on the Proton Collaborative Group Prospective Registry Trial

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Purpose: Assess outcomes of patients enrolled on the Proton Collaborative Group registry trial with recurrent lung cancer reirradiated with proton beam therapy (PBT).

Materials and Methods: Between 2010-2016, 67 patients were reirradiated with PBT at six PCG institutions (Small cell: 7 patients, Non-small cell: 60 patients). Initial lung cancer was treated with conventionally fractionated radiotherapy in 53 (79%) patients (median dose 59.4 Gy, range 30-74 Gy) or stereotactic body radiotherapy in 14 (21%) patients (median dose 50 Gy, range 35-64 Gy/3-5 fractions). Eight (12%) patients received $\geq$2 courses of thoracic irradiation prior to PBT (range 1-3). ECOG performance status was 2 or 3 in 13%. A median PBT reirradiation dose of 60Gy(RBE) was administered (range 30-74Gy(RBE)/1.2-6Gy(RBE)/fraction). Eleven (16%) patients were treated to a palliative dose. Sixteen (24%) and 40 (60%) patients were treated definitively with $>$2Gy(RBE)/fraction or $\leq$2Gy(RBE)/fraction with PBT, respectively. Median time from prior radiotherapy to PBT was 21 months. Twenty (30%) patients received concurrent chemotherapy during PBT.

Results: All patients completed PBT as planned. At a median follow-up of 7.6 months after PBT, median and 1-year overall survival were 13.2 months and 51%, respectively. Median and 1-year progression-free survival were 7.9 months and 26%, respectively. Acute and late grade 3 toxicities (pneumonia, neck pain, fatigue) occurred in 4%. There was no acute or late grade 4 toxicities. One patient died 4.5 months after PBT, of an unclear cause (cardiac complications from reirradiation vs progressive disease).

Conclusion: Reirradiation of recurrent lung cancer with PBT achieves good tumor control with limited toxicity.

PTC17-0195: Multi-Institutional Outcomes of Breast Proton Radiation Therapy: An Analysis of the Proton Collaborative Group Registry

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Purpose: The aim of this study was to determine disease-specific outcomes and toxicities associated with proton therapy for the treatment of breast cancer.

Materials and Methods: The records of 342 breast cancer patients treated with proton radiotherapy in a multi-institutional prospective registry between 2011 and 2016 were analyzed. Six patients with metastatic disease were excluded from analysis. Acute toxicity was defined as any adverse event (AE) occurring within 6 months of the start of radiotherapy. Late toxicity was defined as any event beginning or persisting for 6 months or longer from the start of radiotherapy. All AEs were measured using CTCAE V4.0. Cancer-specific failures were measured from the completion date of radiotherapy.

Results: The median follow-up was 1.2 years (0.2-3.7 years) and 85% for longer than 6 months. Pathological nodal stage was pN1-3 in 68%. Overall, 36 patients received accelerated partial breast irradiation (40Gy RBE), and 300 patients were treated to the intact breast (38%) or chest wall (62%); median of 45Gy RBE (range: 40Gy-66Gy RBE). Deaths occurred in 13.7% of patients. Loco-regional failures were seen in 13.9% of patients and distant failures in 10%. Acute grade 2 toxicity was seen in 67% of patients (with 94% of symptoms resolving within 6 months), and acute grade 3 toxicity was seen in 9.2%. Chronic grade 3 toxicities were seen in 0.5% (n=3) of patients.

Conclusion: This is one of the largest experiences with proton therapy for breast cancer. Although acute grade 2 or higher events were relatively common, symptoms improved within 6 months.

PTC17-0157: MC1631 - A Randomized Trial of 15 vs 25 Fraction Proton Post-Mastectomy Radiotherapy (PMRT): Initial Planning and Acute Toxicity Outcomes

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Purpose: Pencil-beam scanning proton PMRT (PBSP-PMRT) for breast cancer (BC) is being investigated as a strategy to improve the therapeutic ratio by increasing target coverage and reducing dose to organs at risk. Presently, the optimal fractionation for PBSP-PMRT is unknown. Hypofractionation reduced the toxicity of whole breast photon radiotherapy for early stage BC. We instituted a phase II randomized controlled trial to determine the safety of hypofractionated PBSP-PMRT, and herein report preliminary planning and acute toxicity outcomes.

Materials and Methods: Eligibility criteria included age $\geq$ 18 years with non-inflammatory BC resected by mastectomy, with or without immediate reconstruction. Toxicity was graded using CTCAEv4.0. Changes in echocardiographic parameters from baseline to end of treatment were analyzed to assess for subclinical cardiac dysfunction.

Results: Between 5/2016 to 12/2016, 21 patients were randomized to 15 fractions (40Gy[RBE], n=12) or 25 fractions (50Gy[RBE], n=9). Median age was 61, 16 patients were reconstructed (14 expanders, 2 implants) and treatment was left-sided in 16. Table 1 summarizes dose-volume parameters achieved. Grade $\geq$ 2 toxicities included grade 2 dermatitis (15 fractions n=2, 25 fractions n=1) and grade 2 esophagitis (15 fractions n=1). One patient developed cellulitis requiring removal of the expander 6 weeks after PBSP-PMRT completion (15 fractions). No significant differences in echocardiographic parameters (volumes, ejection fraction, or diastolic parameters) between baseline and end of treatment (not shown) or between the two arms (table 2) have been observed.

Conclusion: Hypofractionated PBSP-PMRT is feasible and associated with favorable cardiac sparing and acute toxicity, warranting further study. Enrollment is ongoing.

PTC17-0055: A Retrospective Multicenter Study of Carbon-Ion Radiotherapy for Major Salivary Gland Carcinomas: Subanalysis of J-CROS 1402

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Purpose: A retrospective multicenter study was conducted to assess the clinical outcomes of carbon-ion radiotherapy (CIRT) for head and neck malignancies (Japan Carbon-Ion Radiation Oncology Study Group [J-CROS] study: 1402 HN).In this study, we report on the patient subgroup of major salivary gland carcinoma.

Materials and Methods: Sixty-nine patients treated with CIRT at four Japanese institutions between 2004 and 2014 were analyzed. Fifty-two (75%) patients received CIRT for naive tumors and 17 for recurrent tumors. Thirty-three patients (48%) had adenoid cystic carcinomas, 10 (14%) mucoepidermoid carcinomas, and 26 (38%) had other types. Three patients (4%) had T1 disease, 8 (12%) T2, 25 (36%) T3, and 33 (48%) T4. Thirty-nine (57%) had resectable and 30 (43%) unresectable disease. The median radiation dose was 64 Gy (relative biological effectiveness) in 16 fractions. The median gross tumor volume was 27 cc.

Results: The median follow-up period was 32.7 months. Three- and five-year local control rates and overall survival rates were 81% and 74% and 94% and 82%, respectively. Three-year and five-year disease-free survival rates were 51% and 51%, respectively. Seven patients developed local recurrences, five lymph-node metastases, and 25 distant metastases. Regarding acute adverse reactions, seven patients had grade 3 mucositis and seven grade 3 dermatitis. Regarding late effects, one patient had grade 3 dysphagia and one had a grade 3 brain abscess. No grade 4 or worse late reactions were observed.

Conclusion: Our study indicated that definitive CIRT was effective with acceptable toxicity for major salivary gland carcinomas.

PTC17-0024: Clinical Outcomes of Carbon-Ion Radiotherapy with Concurrent Chemotherapy for Locally Advanced Adenocarcinoma of Uterine Cervix in Phase 1/2 Clinical Trial

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Purpose: This study evaluates the toxicity and efficacy of carbon-ion radiotherapy (C-ion RT) with concurrent weekly cisplatin (CDDP) for locally advanced adenocarcinoma of uterine cervix in a phase 1/2 clinical trial.

Materials and Methods: The treatment consisted of whole-pelvic irradiation of 36.0 Gy [relative biological effectiveness (RBE)] in 12 fractions and local boost with dose escalation from 32.0 to 38.4 Gy (RBE) in 8 fractions with concurrent weekly CDDP of 40 mg/m2. The phase 1 endpoint was to determine the maximum-tolerated dose of C-ion RT. The phase 2 was to evaluate the late toxicities and efficacy using the dose which determined in phase 1 component.

Results: Between April 2010 and March 2014, 33 patients were enrolled in this trial. Two patients did not receive chemotherapy because of worsened bone-marrow function; 31 patients were analyzable in the present study (Table 1). Only a patient had grade 3 or worse acute toxicities in phase 1 component. Thus, 74.4 Gy (RBE) was determined to use for phase 2 component. In phase 2 component, 2 patients had grade 3 or worse gastrointestinal tract (GI), both of the 2 cases had some damages to GIs (repeated laser coagulation or peritonitis caused by appendicitis) after the treatment (Table 2). The 2-year local control, progression free survival, and overall survival rate were 71%, 56%, and 88%, respectively.

Conclusion: C-ion RT with concurrent weekly CDDP for adenocarcinoma of uterine cervix was accomplished without severe toxicities except in 2 cases. The results support continued investigation and analysis to confirm therapeutic efficacy.

Pediatric and Sarcoma

PTC17-0474: Relation Between Biologic Dose Hotspots and Radiation-Induced Imaging Changes in Pediatric Brain Tumor Patients

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Purpose: To investigate correlations between post-RT imaging changes and proton biologic dose (BD) for pediatric brain patients treated with spot-scanning proton therapy.

Materials and Methods: Proton treatment began at our institution in 5/2015. 9 pediatric brain tumor patients treated at our institution were randomly selected for this study. The prescription was 54 Gy in 30 fractions. In each case, the physical dose (PD), dose-averaged LET (LETd) and BD distributions were computed with a GPU-based Monte Carlo. The BD was calculated from LETd assuming a linear relation: BD=1.1*PD*(0.08*LETd+0.88). Follow-up imaging was obtained for all patients every 1-3 months for 1 year. T2-Flair and T1-gadolinium contrast enhanced images were fused with treatment planning CT. Contouring was done on the first scan that demonstrated imaging changes. Deformable dose accumulation was applied when required. V105% PD, V110% PD, V105% BD and V110% BD were evaluated. PD was scaled with a constant RBE of 1.1. Hotspot volumes outside the CTV were evaluated as a crude measure of the high-dose irradiation of normal tissue.

Results: Four patients displayed radiation-induced imaging changes. Table 1 shows the PD and BD hotspot volumes. Fig. 1 displays the V105% BD outside the CTV; patients with imaging changes are in red. Below V105% BD=19cc, only one in 6 patients had post-RT changes. Above 19cc, all patients displayed radiation-induced imaging changes. The dependence on V105% PD was less prominent.

Conclusion: There appears to be a relationship between BD hotspot volumes and post-RT changes. More data is required to confirm the observed trends.

PTC17-0437: Esophagitis in the Multimodality Treatment of Thoracic Ewing Sarcoma: Incidence, Risk Factors, and Management

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Purpose: To analyze the incidence, risk factors, and management of esophagitis in pediatric patients with Ewing sarcoma of the thoracic spine and chest wall treated with chemotherapy and proton therapy (PT).

Materials and Methods: This study was a single-institution review of patients between <21 years old treated with PT between 2006-2016. Medical records were reviewed for patient and treatment characteristics.

Results: Twelve of 37 patients (32%) who received chemoradiation developed acute esophagitis characterized by dysphagia +/- odynophagia. Four, 7, and 1 patient had CTCAE grade 2,3, and 4 esophagitis, respectively. Twenty-five percent of patients lost >10% of their body weight. Patients who received concurrent ifosfamide/etoposide had higher incidence of esophagitis than those who received concurrent vincristine/cyclophosphamide (56% vs 25%, p=0.01). Neutropenia (ANC < 500 K/mcL) was associated with an increased risk of esophagitis (60% vs 14%, p<0.01). Although esophagitis was observed in 3 patients who received little or no PT to their esophagus, PT significantly contributed to the incidence when maximum esophageal dose was > 47Gy (69% vs 5%, p<0.0001) and esophageal D5cc was > 15Gy (67% vs 9%, p<0.001). All 12 patients with esophagitis were initially managed with oral opioid analgesics. Nine patients with persistent symptoms received subsequent fluconazole for empiric fungal treatment and each had decreased need for opioid analgesics within 2-5 days.

Conclusion: Approximately a third of patients with Ewing sarcoma of the thoracic region will develop acute esophagitis. Our study provides practical dosimetric guidelines for PT planning and suggests an infectious component to the process that responds to standard antifungal therapy.

PTC17-0311: Carbon Ion Radiotherapy for Unresectable Bone and Soft Tissue Tumors: A Multi-Institutional Retrospective Analysis of 764 Cases (J-CROS 1401 BS)

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Purpose: To retrospectively evaluate the feasibility and efficacy of carbon ion radiotherapy (CIRT) for patients with unresectable bone and soft tissue tumors treated in 4 institutions of Japan Carbon-ion Radiation Oncology Study Group (J-CROS).

Materials and Methods: Patients with pathologically-proved, unresectable bone or soft tissue tumors treated with CIRT as a definitive treatment between November 2003 and December 2014 were enrolled in this study. Patients with distant metastasis were excluded. Survival outcomes were estimated using Kaplan-Meier analysis.

Results: A total of 764 patients were analyzed. The median age at the CIRT was 59 years. Median follow-up time was 41.4 months (range, 1.4-130.4 months). They received CIRT with median dose of 70.4 Gy (RBE) (range, 57.6-79.2 Gy (RBE)). The 3- and 5-year overall survival rates (OS) in all patients were 80% and 65%, and local control rate were 77% and 65%, respectively. The 3- and 5-year OS of 572 patients with bone tumor were 79% and 68%, and those of 192 patients with soft tissue sarcoma (STS) were 69% and 55%. The 5-year OS by disease were 83% in patients with sacrococcygeal chordoma (n=223), 39% with pelvic osteosarcoma (n=58), 43% with pelvic chondrosarcoma (n=50), 40% with retroperitoneal STS (n=30), 72% with STS of head and neck (H&N) (n=28), and 64% with osteosarcoma of H&N (n=12), respectively.

Conclusion: The results of this first multi-institutional study showed that CIRT must be an alternative treatment option for patients with unresectable bone and soft tissue tumors.

PTC17-0144: Cerebral Glucose Metabolism in Craniopharyngioma Patients 3 Years After Proton Therapy

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Purpose: We investigated brain injury in children receiving craniopharyngioma treatment with longitudinal fluorodeoxyglucose positron emission tomography (FDG PET) imaging.

Materials and Methods: Treated with surgery and proton therapy (54 CGE in 30 fractions) between 2011 and 2014 in a prospective trial, 38 patients (aged 2-19 years) completed baseline, 18-month, and 36-month FDG PET studies as a part of functional integrity measures. Tracer uptake in each of 63 anatomical brain regions was computed after 3D warping to Talairach coordinates and compared to 99% prediction intervals of an age-associated normal uptake distribution of 132 children to determine abnormality.

Results: Overall, most patients (29 of 38) showed stable patterns of cerebral glucose metabolism from baseline to 36-month PET. Among them, 20 were consistently normal and 9 were persistently abnormal with 4-13 hypometabolic regions. Patterns observed in the remaining 9 patients were improvement from extensive hypometabolism at baseline in 5 of 38 children and increasing hypometabolic defects in 4. The latter is hypothesized to be related to vascular injury and craniotomy after proton therapy. Hypometabolism was most commonly seen on 36-month PETs in right hippocampus (9 of 38), right straight gyrus (8), caudate nucleus (7), and fusiform gyrus (6). For 16 children who received no or minimally invasive surgeries, 13 had consistently normal glucose uptake and 3 had focal metabolic defects lasting from baseline.

Conclusion: Proton therapy did not appear to exacerbate pre-existing metabolic defects in this cohort. Persistent abnormalities from surgery and mass effects should be considered when evaluating toxicity profiles of proton therapy.

PTC17-0100: Dosimetric Comparison of Volumetric Modulated Arc Therapy Versus Pencil Beam Scanning Proton Therapy for Children Treated for Wilms' Tumor

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Purpose: Dosimetric comparison of volumetric modulated arc therapy (VMAT) and pencil beam scanning proton therapy (PBS-PT) in patients with Wilms' tumor (WT) undergoing flank irradiation after nephrectomy.

Material and Methods: Dose distributions obtained by VMAT and PBS-PT from 15 patients (3.5$\pm$2.0 years) with prescription doses (PD) ranging between 10.8-25.2 Gy were reviewed. VMAT plans were conventionally optimized using a uniform safety margin of 5 mm around the clinical target volume (CTV) to account for intra- and inter-fraction patient set-up uncertainties. PBS-PT plans were CTV-based robustly optimized accounting for 5 mm patient set-up and 3% proton range uncertainties. Dose-volume metrics were computed for both plans types to assess CTV coverage and organs at risk (OARs) sparing, with $P<0.05$ (Wilcoxon) considered significant.

Results: For both techniques, the CTV coverage (D98% $>$ 95%PD) was fulfilled. However, the minimum CTV coverage (V95%) was higher for PBS-PT [99.9 - 100%] when compared to VMAT [98.2 - 100%]. Significant better sparing of the OARs was achieved with PBS-PT (Table 1). Maximum reduction of the median dose (D50%) given to the OARs was 44%, 65% and 53% of the PD for the contralateral kidney, liver and spleen, respectively. In cases with OARs adjacent to the CTV, the gain with protons was smaller.

Conclusion: When compared to VMAT, PBS-PT presents equal or better target coverage. In addition, a significant better sparing of the OARs is achieved with PBS-PT. Thus, chances of reducing radiotherapy side effects might increase with PBS-PT over VMAT.

PTC17-0523: Initial Outcomes of International Pediatric Patients with CNS Tumors Treated at ProCure Oklahoma City

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Purpose: Proton therapy can spare substantial normal tissue from radiation exposure as compared to x-ray based radiotherapy. This is of particular importance in pediatric patients with brain tumors. As it can take many years for a proton center to be developed, several countries have programs in place for their citizens to be sent abroad to the US for proton radiotherapy.

Materials and Methods: We undertook an analysis of the international patients with CNS tumors that have been treated at ProCure Oklahoma City. We identified 99 patients who were treated between 2011 Jun 01 and 2016 Aug 02.

Results: The histology of the tumor types treated are listed in Table 1. The median fractions and radiation dose and delivered was 30 (range 25 - 39) and 54.12 Gy(RBE) (range 45.0 – 78.0 Gy(RBE)). Of the 60 living patients who have 12 months' minimum of follow-up, the crude overall survival and progression-free survival is 88.3% and 85.0%, respectively, at a median follow-up of 23 months (11 – 58 months). Acute and late toxicities are listed in Table 2. There were a total of 28 post-radiotherapy grade 2 toxicities, and no post-radiotherapy grade 3 toxicities.

Conclusion: Proton radiotherapy is an effective and safe modality of radiotherapy for pediatric patients with CNS tumors. A systematic approach for significant international patient referrals abroad to the US while maintaining excellent disease control and follow up is feasible.

Gastrointestinal Organs and Breast

PTC17-0515: Standardized Metric for Plan Evaluation in Breast Cancer Radiotherapy Creates Objective Measurement of Plan Quality, Enables Objective Comparison of Modalities

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Purpose: Plan assessment remains largely subjective. In this study, advanced plan-scoring methods for breast cancer are introduced to (1) study variability and achievable benchmarks in treatment planning and (2) compare a population of proton and photon plans designed for controlled patient datasets.

Materials and Methods: A breast cancer scoring method was developed, modeled on the NSABP-B51/RTOG-1304 protocol, including organ-at-risk (OAR) constraints and target coverage goals. Performance bins ranged from ideal (full target coverage; no OAR dose) to unacceptable (aligned with major deviation in the protocol). Deidentified datasets for 3 patients (intact breast, postmastectomy without reconstruction, postmastectomy with expander reconstruction) were available for download. Plan-scoring tools were implemented via a cloud-based web interface to allow participants to score plan iterations and submit a final plan. On a sliding scale, points were awarded according to performance versus objectives for 21 metrics.

Results: This scoring method was confirmed with pilot data using treatment plans submitted by 4 planners (proton and photon) to establish proof of concept. For the intact breast case, scores ranged from 84.19–133.94 points out of 150. Using this scoring method, an international study is being designed in which treatment plan data will be anonymously collected, with the goal of $\geq$50 proton and $\geq$50 photon plans for each of the three cases. Analysis of plan quality and variation will be done, and modalities compared objectively.

Conclusion: Objective analysis of plan quality is a powerful and important way to determine and compare the capabilities of planners, planning systems, and modalities.

PTC17-0263: Carbon-Ion Radiotherapy for Stage I Breast Cancer

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Purpose: The study of carbon-ion RT (CIRT) for patients with stage I breast cancer were analyzed.

Materials and Methods: The candidates for CIRT are the patients with low-risk stage I breast cancer. The patients who had minor variance from eligible criteria of clinical trial and/or refused to enroll clinical trial were treated with advanced medical care. Tumors located less than 5 mm from the skin are ineligibility. Total dose is 48.0 Gy(RBE), 52.8 Gy(RBE) and 60.0 Gy(RBE) in 4 fractions within one week, respectively.

Results: From April 2013 to November 2016, 22 cases were treated. Patients' age ranged from 44 to 81 years old, with a median of 66 years old. Tumor sizes were 4 to 20 mm, with a median of 12 mm. There were 3 cases of 48 Gy(RBE), 5 cases of 52.8 Gy(RBE) and 14 case of 60 Gy(RBE) were treated. No adverse reactions in normal tissue were observed except for grade 1 acute skin reaction of CTC-AE v4.0 in 13 cases. The follow-up period ranged from 3 to 43 months, with a median of 26 months.One patient with basal subtype tumor had recurred local and axillary lymph node was successfully salvaged by surgery. Other 21 tumors are successfully controlled.

Conclusion: CIRT for patients with stage I breast cancer seems to be safe and effective, and potential as one of the minimally invasive treatment has been suggested.

PTC17-0198: Short -Course Carbon-Ion Radiotherapy for Hepatocellular Carcinoma

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Purpose: To evaluate the safety and efficacy of short-course carbon ion radiotherapy (CIRT) for hepatocellular carcinoma (HCC).

Materials and Methods: Between April 2003 and July 2015, 196 patients with HCC underwent 2- fraction CIRT. The median age was 73 years old. 128 were males and 68 were females. 154 the patients were suffering from hepatitis C or hepatitis B viral infection. The degree of liver impairment was judged as Child-Pugh grade A in 178 patients, B in 18. The maximum tumor diameter ranged from 1.3 to 14 cm, with a median of 3.6cm. 163 patients had a solitary lesion and 18 had multiple lesions. The total dose was escalated from 32 Gy (RBE) up to 48 Gy (RBE). We evaluated the toxicity, local control and overall survival.

Results: There were no cases of grade 4 or higher toxicities. Local control rates were 94%, 84% and 83% at 1, 3 and 5 years after CIRT, respectively. There was significant difference in local control rates according to total dose ($P<0.001$). The 1, 3, 5-year overall survival rates were 95%, 64%, and 39%, respectively.

Conclusion: Short-course high-dose CIRT is a promising treatment for hepatocellular carcinoma.

PTC17-0189: Single-Institutional Experience with Carbon-Ion Radiotherapy for Pancreatic Cancer

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Purpose: To evaluate the efficacy and toxicity of carbon-ion radiotherapy (C-ion RT) for pancreatic cancer.

Materials and Methods: 59 pancreatic cancer patients treated with definitive C-ion RT from 2014/04 to 2015/12 at our institution were retrospectively analyzed. Number of patients with UICC stage IIA/ IIB/ III/ IV were 9/ 3/ 44/ 3. 44 patients (75%) were confirmed as adenocarcinoma pathologically. C-ion RT was performed with 55.2 Gy (RBE) at 12 fractions. Induction chemotherapy was performed in 46 patients and the median duration time was 3 months. Concurrent chemotherapy with gemcitabine and/or S-1 was performed in 54 patients. Anti tumor effects and toxicities were evaluated using RECIST v1.1 and CTCAE 4.0. Survival time was calculated from the initiation of C-ion RT to progression or death. To compare with previous reports, we focused on unresectable locally advanced pancreatic ductal adenocarcinoma (LA-PDAC) (n=34) and also analyzed survival outcome.

Results: The median follow up time was 19.3 months. Freedom from local progression and overall survival in all patients were 83% and 78% at 1 year and 81% and 60% at 2 year, respectively. Two year overall survival in LA-PDAC was 61%. Five patients experienced acute G3 toxicities: neutropenia in 2, gastric ulcer/bleeding in 1, anorexia in 1, pneumonitis due to gemcitabine in 1. One patient had a late G3 gastric bleeding. There was no G4/5 toxicity.

Conclusion: C-ion RT for pancreatic cancer is considered to be effective and safe for the treatment of pancreatic cancer.

PTC17-0063: Carbon-Ion Radiotherapy for Pancreatic Cancer in Patients Aged 80 Years or Older

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Purpose: The purpose of our study was to evaluate the efficacy and safety of carbon-ion radiotherapy (C-ion RT) for pancreatic cancer in patients aged 80 years or older.

Materials and Methods: We retrospectively analyzed patients aged 80 years or older with pancreatic cancer who underwent C-ion RT between June 2011 and April 2016. Clinical outcomes included overall survival (OS), local control (LC), progression-free survival (PFS), and toxicity. Toxicity was evaluated using CTCAE version 4.0.

Results: In total, 30 patients were included in this study. Median age at time of C-ion RT was 83 years (range, 80–97 years). Definitive C-ion RT was selected due to age and/or co-morbidities in 11 patients, presence of locally advanced and unresectable diseases in 11, and patient refusal of surgery in 8. The median follow-up period from the initiation of C-ion RT for all patients was 11.4 months (range, 1.0–46.7 months). The OS, LC and PFS rates were 67.5%, 49.5% and 35.2% at 1 year and 48.2%, 24.8% and 19.5% at 2 years, respectively, with a median OS of 15.8 months. With regard to toxicity, acute grade 3 cholangitis was seen in 3 patients and acute grade 3 leukopenia in 1. No patients had late grade 3+ toxicity.

Conclusion: C-ion RT can be performed on patients aged 80 years or older with pancreatic cancer with minimal toxicity and fair treatment outcome, and may be considered an alternative for patients who are not candidates for resection due to age, co-morbidities, and/or locally advanced disease.

PTC17-0021: A Multi-Institutional Analysis of Neoadjuvant Radiation Modality and Toxicity in Trimodality Management of Esophagus Cancer in Elderly Patients

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Elderly patients had the greatest increase in incidence of esophageal adenocarcinoma over the past 4 decades. We evaluated the impact of radiotherapy (RT) modality on toxicity of trimodality therapy for esophagus cancer in elderly patients.

We evaluated 571 patients treated with trimodality therapy at 3 high-volume U.S. cancer centers from 2007 to 2013. 202 of 571 (35%) patients were $\geq$ 65 years and classified as elderly. 87 patients received 3DCRT, 73 patients received IMRT, and 42 patients received proton (PRT). Toxicity and treatment modality was compared using univariate (UVA) and multivariable (MVA) logistic analyses.

Higher rates of postoperative cardiac (UVA: OR 2.2, $p<0.001$; MVA: OR 2.07, $p=0.004$) and pulmonary (UVA: OR 2.0, $p<0.001$; MVA: OR 2.03, $p<0.001$) complications were observed in age $\geq$ 65 years. 90-day postoperative mortality was higher in the elderly (5.4 vs 2.2%, $p=0.049$). Compared to IMRT and PRT, 3DCRT increased the risk of cardiac toxicity by 2 and 3 fold, respectively. Compared to PRT, but not IMRT, 3DCRT increased the risk of postoperative pulmonary toxicity by 3 fold. Rates of postoperative pulmonary complications were 46%, 39.7%, and 16.7% for 3DCRT, IMRT, and PRT, respectively ($p=0.02$). Rates of postoperative cardiac complication were 36.8, 17.8%, and 11.9% for 3DCRT, IMRT, and PRT, respectively (0.002).

Elderly patients are at an increased risk for postoperative complications. Reduction in toxicity with PRT is likely related to less cardiopulmonary irradiation. Improved radiation conformality may be of greater importance for elderly patients secondary to decreased cardiopulmonary reserve and additional comorbidities.

Head and Neck and Genitourinary Organs

PTC17-0528: Feasibility of Rectal Spacer Hydrogel in Proton Therapy for Large Prostate Glands (>80 Cc)

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Purpose: A phase III study demonstrated a dosimetric benefit of rectal spacer hydrogel (GEL) in lowering rectal dose and decreasing the risk of radiation induced gastro-intestinal (GI) toxicity in prostate cancer patients with glands up to 80 cc undergoing definitive radiotherapy. In this study, we analyzed the feasibility of employing GEL in patients with glands >80 cc treated with fiducial based image-guided pencil beam scanning proton therapy to 78 $Gy_{(RBE)}$ in 39 fractions.

Materials and Methods: 300 patients with prostate cancer underwent proton therapy with GEL between 04/2015 and 09/2016, of which 26 had glands >80 cc; 14 (>80-100cc) and 12 (>100cc). Mean follow up for these 26 patients was 12 months (range 3-20). Mean IPSS score was 9 (range 1-22). GEL placement was performed as an outpatient procedure under local numbing in all cases.

Results: Prostates measuring 80-100cc had a mean midgland recto-prostatic GEL separation of 1.29 cm with mean rectum V70, V60, and V50 of 1.2, 3.6 and 7.2%, respectively. Larger glands (>100cc) had a mean separation of 1.09 cm with rectum V70, V60, and V50 of 1.1, 3.8 and 7.6%. Bladder V70 was 10.7% and 14.9%, respectively. All patients tolerated treatment well without any grade 2 adverse GI or GU events.

Conclusion: GEL placement was successfully performed in all patients with prostates >80 cc without any complications, resulting in reproducibly satisfactory midgland recto-prostate separation and very low V70, V60, and V50 rectal doses.

PTC17-0448: Induction Chemotherapy Followed by Concurrent Chemotherapy and Proton Beam for Sinonasal Undifferentiated Carcinoma

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Purpose: The optimal treatment of sinonasal undifferentiated carcinoma (SNUC) remains to be defined given its aggressiveness and dismal outcome with traditional treatment. We examined the treatment outcomes of SNUC treated with combined proton beam with concurrent chemotherapy +/- induction chemotherapy.

Materials and Methods: Between 2005 and 2016, 15 patients with SNUC were treated at our institution. All patients had T4 disease, with 20% had nodal involvement and 87% with orbital invasion. Forty-seven percent of patients underwent induction chemotherapy followed by concurrent chemoradiotherapy (sequential group) and 53% underwent or concurrent chemoradiotherapy alone. All patients underwent proton beam for the primary site and upper neck, and photon irradiation for the lower neck. The median dose to the primary site was 70Gy(RBE). Locoreigonal control, freedom from distant metastasis, disease-free survival, and overall survival were estimated by the Kaplan-Meier method.

Results: With a median follow-up of 25 months, there were 2 local, 2 regional, 4 distant, and 5 dural-leptomeningeal failures. The 2-year locoregional control rates were 100% and 60% (95%CI:33%-100%) for the sequential and concurrent alone groups, respectively, (p=0.10). The 2-year overall survival was 100% for the sequential group and 58% (95%CI:31%-100%) for the concurrent group (p-value=0.03). The 2-year distant-metastasis-free survival was 83% (95%CI:58%-100%) and 31% (95%CI:10%-96%) for the sequential and concurrent group, respectively (p-value= 0.03). Furthermore, the sequential group has a 2-year disease-free survival rate of 100% compared with 58% (95%CI:1%-100%) for the concurrent group (p=0.02).

Conclusion: Induction chemotherapy followed by concurrent chemotherapy and proton beam results in promising outcome in patients with SNUC.

PTC17-0429: Re-Irradiation Employing Intensity Modulated Proton Stereotactic Ablative Radiotherapy (IMP-SABR)

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Purpose: Prudent use of SABR in salvage or palliative re-irradiation may lead to clinically desirable outcomes while decreasing the risk of normal tissue toxicity. IMP-SABR is an appealing re-irradiation technique as it may allow improved target coverage while minimizing undesirable dose to the adjacent organs at risk. Herein, we report our initial IMP-SABR re-irradiation experience.

Materials and Methods: All patients treated with IMP-SABR ($\leq$ 5 fractions and $>$ 700 cGy RBE/fraction) were reviewed. All patients were treated on a Hitachi PROBEAT-V proton therapy system with daily 2D/3D kV registration. Verification CTs were performed at the treating physician's discretion.

Results: Since June 2015, 13 patients received IMP-SABR for re-irradiation. Median age was 54 (40–73) and mean follow up was 3.4 months (0-10). Mode dose and fraction were 30Gy and 3, respectively. Eight patients were treated with curative intent. Three of four patients with pain had improvement following palliation. For those with available follow up, local control was 100%. Table 1 summarizes patient and treatment characteristics. Toxicities include grade 2 pain (2) and compression fracture of the re-irradiated spine (1).

Conclusion: IMP-SABR may be a safe option for re-irradiation in both curative and palliative situations. Toxicity is favorable, however, longer follow is necessary.

Patient	IMP-SABR (Gy/fraction)	Site
1	30/3	Sacrum
2	36/3	Pubic bone
3	50/5	Nasopharynx
4	30/3	T12
5	30/3	Bile duct
6	27/3	Supraclavicular LN
7	30/3	Sacrum
8	39/3	Pubic bone
9	36/3	T1-4
10	36/3	S1
11	50/5	Parotid
12	30/3	Liver
13	50/5	Skull base

PTC17-0305: Active Scanning Carbon Ion Radiotherapy (CIRT) for Malignant Mucosal Melanoma: Preliminary Results at CNAO (National Center of Oncologic Hadrotherapy) Experience

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Purpose: to evaluate the preliminary results of patients with malignant mucosal melanoma tretead with active scanning carbon ion radiotherapy.

Materials and Methods: Since June 2013 to January 2016, 16 patients (pts) with diagnosis of mucosal malignant melanoma were treated at CNAO. Primary tumors were located in the sinonasal cavity in 11 pts, oral cavity in 2 pts and oropharynx, lacrimal duct and nasopharynx 1 patient each. Stage III (7 pts) and stage IVa (9 pts). Four pts were only previously biopsied; 12 pts underwent surgery and referred because of gross tumor residual or recurrence. Median time between surgery and CIRT was 4.5 months (range 1.2-30.7 months). CIRT was delivered to the total dose of 68,8 Gy RBE (16 fractions, 4.3 Gy RBE/fraction, 4 fractions/week). Follow-up was performed with a clinical examination and MRI every 3 months; toxicity was scored according to CTCAE 4.0.

Results: No G4 toxicity. No G3 acute skin toxicity. G3 acute mucosal toxicity in 3 pts. With a median follow up of 13 months (range 2 – 30) the actuarial 1y local control was 79.5%, 1y overall survival was 74.5% and 1y distant progression free survival was 54%. One patient developed G3 hypoacusis (expected toxicity). Six pts developed G2 late toxicity: xerostomia (2 pts), trigeminal neuralgia (3 pts) and trismus (1 patient).

Conclusion: Although the limited number of pts and the short follow up, handrontherapy with active scanning carbon ion provides promising results with low toxicities. More data and longer follow up are requested.

PTC17-0256: Visual Toxicity After Proton Therapy for Sinonasal Cancer

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Purpose: We report on the rate of serious vision loss and associated dosimetric factors in patients treated with proton therapy (PT) for sinonasal cancer.

Materials and Methods: Ninety-seven patients (188 eyes/optic nerves (ONs)) were included in the analysis. Nearly all received twice-daily PT (median dose, 73.6 at 1.2 Gy(RBE)/fraction) with 76% receiving chemotherapy. Median follow-up was 2.7 years. Visual toxicity included visual acuity 20/200+, visual field deficits, or self-reporting of vision loss by phone or at clinical follow-up. Dose-effect was assessed by logistic regression.

Results: There were 4 monocular events (including keratopathy, optic neuropathy, and retinopathy) yielding a crude rate of 4%/patient or 2.1%/eye, all occurring in patients with orbital invasion. For eyes with toxicity, the average Dmax, D33%, and median ON and retina doses were 77.0, 70.0, and 66.8 Gy(RBE) and 76.7, 51.0, and 40.3 Gy(RBE), respectively. For all eyes, the average Dmax, D33%, and median ON and retina doses were 59.4, 42.0, and 37.5 Gy(RBE) and 61.9, 27.5, and 19.8 Gy(RBE), respectively. Multiple dosimetric parameters correlated with toxicity, including the D33%.

Conclusion: Hyperfractionated PT for sinonasal cancer resulted in rare visual toxicity. Dose-effect models revealed multiple significant dosimetric parameters, but conclusions regarding dose-effect are limited by a low event rate. We recommend the following DVH goals for OARs that are within/adjacent to high-risk target volumes: Dmax and D33% of 65 and 55 Gy(RBE) for the ON/chiasm, and 70 and 40 Gy(RBE) for the retina.

PTC17-0187: A Multi-Institutional Retrospective Study of Carbon-Ion Radiotherapy (CIRT) for Squamous Cell Carcinoma of the Head and Neck

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Purpose: A multi-institutional retrospective study (Japan Carbon-Ion Radiation Oncology Study Group [J-CROS] study: 1402 HN) was conducted to analyze the treatment outcomes of carbon-ion radiotherapy (CIRT) for head and neck cancer among carbon-ion facilities. In this study, we present the results of patients with squamous cell carcinoma (SCC) of the head and neck.

Materials and Methods: A total of 54 patients treated between June 2004 and September 2014 were included. Patient median age was 59 years. Tumor sites included nasal cavity and paranasal sinuses (56%), auditory canal (20%), oral cavity (9%), and others (15%). T-classifications were T4 in 32 (59%), T3 in 10 (19%), T2 in 6 (9%), T1 in 3 (6%), and unclassified in 4 (7%) patients. The median total dose was 65 (range, 57.6-70.4) Gy (RBE) in 26 (range, 16-35) fractions.

Results: The median follow-up time was 19.5 (range, 6-126) months for all patients and 29.5 (range, 6-126) months for survivors. The 3-year overall survival (OS), progression-free survival (PFS) and local control (LC) rates were 60%, 46% and 55%, respectively. The log-rank test revealed that nasal cavity and paranasal sinuses were significantly associated with better LC. The 3-year LC rate for patients with nasal cavity and paranasal sinus carcinoma were 72%. Grade 3 or higher acute toxicities were observed in 14 patients (26%). Ten patients (19%) experienced grade 3 or higher late toxicities.

Conclusion: Treatment results of SCC of the nasal cavity and paranasal sinuses were satisfactory compared with conventional methods. Those tumors are good indication of CIRT.

PTC17-0173: Sinonasal Cancer Patients Treated with Proton Therapy: The Proton Collaborative Group (PCG) Experience

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Purpose: Report the outcomes of sinonasal cancer patients treated with proton therapy (PT) by the Proton Collaborative Group.

Materials and Methods: Eighty-eight patients with sinonasal tumors who received PT were identified for the present IRB approved analysis. Median age was 57.9 years (range, 15.7 – 88.0). Most common histology was squamous cell carcinoma (SCC) in thirty two patients (36%), and most common T stage was T4 in 36 (41%) patients. Patients received PT either as definitive (n=13, 15%), adjuvant (n=27, 31%), boost (n=21, 24%), or as a retreatment (n=27, 31%). Median PT dose was 50.2 Gy (RBE) (range, 10 – 75.8). Twenty three patients (26%) received platinum based chemotherapy. Statistical analyses of outcomes were calculated using the Kaplan-Meier method.

Results: Median follow-up for surviving patients was 21 months (range, 2.2 – 317). The 3-year OS, DFS, LC and DMFS were 88%, 76%, 78% and 79% respectively. With respect to SCC histology, the 3-year OS, DFS, LC and DMFS were 87%, 95%, 95% and 93% respectively. A total of 13 patients (15%) experienced recurrent disease, 7 local (8 %), 1 regional (1%) and 6 (7%) distant metastasis. There were 14 acute grade 3 toxicities. Radiation dermatitis (n=4, 29%), mucositis (n=4, 29%), and fatigue (n=3, 21%) were the most common experienced. Late toxicity occurred in 15% of the patients, with only one grade $\geq$ 3 toxicity consistent of a grade 4 unilateral vision loss. No patients developed symptomatic brain necrosis.

Conclusion: PT achieved favorable outcomes with an acceptable toxicity profile in this challenging group of patients.

PTC17-0110: A Multi-Institutional Retrospective Study of Carbon-Ion Radiotherapy for Adenoid Cystic Carcinoma of the Head and Neck

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Purpose: A multi-institutional retrospective study (Japan Carbon-ion Radiation Oncology Study Group [J-CROS] study: 1402 HN) was conducted to analyze the treatment outcomes of carbon-ion radiotherapy (CIRT) for head and neck cancer among active carbon-ion facilities in Japan. In this study, we present the results of patients with adenoid cystic carcinoma (ACC).

Materials and Methods: A total of 289 patients treated between December 2003 and December 2014 at four institutions were included in this study. Patient median age was 58 (range, 12-83) years. Tumor sites included nasal cavity and paranasal sinuses (42%), nasopharynx and oropharynx (19%), oral cavity (12%), major salivary glands (12%) and others (15%). T-classifications were T4 in 200 (69%), T3 in 45 (16%), T2 in 22 (8%), T1 in 15 (5%), and unclassified in 7 (2%) patients. The median total dose was 64 (range, 55.2-70.4) Gy (RBE) in 16 (range, 12-32) fractions.

Results: The median follow-up time was 30 (range, 2-118) months. The 2-year/5-year overall survival, progression-free survival and local control rates were 94%/74%, 68%/44% and 88%/68%, respectively. Forty-three patients (15%) experienced grade 3 or higher late toxicities. Osteonecrosis of the jaw bone was the most common late toxicity. Two patients treated for nasopharyngeal ACC developed grade 5 hemorrhage caused by ulceration at the tumor site.

Conclusion: The multi-institutional retrospective study conducted by J-CROS showed that CIRT was effective in achieving favorable local control and survival in ACC of the head and neck.

PTC17-0027: Prognostic Factors in High-Risk Prostate Cancer After Carbon-Ion Radiotherapy Combined with Long-Term Androgen Deprivation Therapy

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Purpose: To determine the prognostic factors for biochemical recurrence (BR) and mortality in patients with high-risk localized prostate cancer after carbon-ion radiotherapy (CIRT) combined with long-term androgen deprivation therapy (LTADT).

Materials and Methods: A total of 1247 patients were enrolled in three phase II clinical trials of fixed-dose CIRT between 2000 and 2013. Excluding T4 disease, 614 patients received CIRT combined with LTADT for high- or very-high-risk disease, according to the National Comprehensive Cancer Network (NCCN) classification system.

Results: Median follow-up time was 78.7 months, and 5-year rates of BR-free, prostate cancer-specific survival, and overall survival were 90.4% (95% confidence interval [CI]: 87.6 - 92.7), 98.5% (95% CI: 97.2 - 99.2), and 94.7% (95% CI: 92.8 - 96.5), respectively. T3a/b disease, Gleason score (GS) 9-10, percentage of positive biopsy cores (PPCs) $>$ 75%, and age $>$ 75 years had a significant impact on BR. Moreover, patients with T3b disease, GS 9-10, and PPCs $>$ 75% had significantly higher prostate cancer-specific mortality ($p = 0.007$, $p = 0.009$, and $p = 0.015$, respectively) and overall mortality ($p = 0.035$, $p = 0.025$, and $p < 0.001$, respectively), on multivariate analyses.

Conclusion: Prognostic factors for BR and mortality were identified. Patients with T3b disease, GS 9-10, and PPCs $>$ 75% should be considered to have very-high-risk disease requiring a new treatment strategy.

Motion Management

PTC17-0488: Efficient Interplay Effect Mitigation for Proton Pencil Beam Scanning by Spot-Adapted Layered Repainting Evenly Spread over the Full Breathing Cycle

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Purpose: To develop a practical repainting method for efficient interplay effect mitigation in proton pencil beam scanning (PBS) and implement the method at a ProBeam facility.

Materials and Methods: A new flexible repainting scheme that allows spot-specific numbers of repaintings that are spread evenly over the breathing cycle (here assumed to be 4s) was developed. Twelve fields from five thoracic/abdominal PBS plans were delivered three times with the new repainting scheme to an ion chamber array on a motion stage: Once static and twice with 4s, 3cm peak-to-peak sinusoidal motion (with different starting phases). For comparison, all dose measurements were repeated with no repainting and 8 repaintings. For each motion experiment, the 3%/3mm gamma pass rate was calculated using the motion-convolved static dose as reference. Simulations were first shown to reproduce the experiments and then used to extend the study to other motions and more fractions.

Results: The new repainting scheme had significantly higher gamma pass rates than conventional repainting. Simulations reproduced the experimental gamma pass rates with 1.3% root-mean-square error and demonstrated largely improved pass rates with the new repainting for all investigated motions. 4D dose reconstruction for a pancreas case showed more uniform dose with fewer interplay effects with the new repainting scheme.

Conclusion: A novel repainting strategy for efficient interplay effect mitigation was proposed and implemented. It was shown to be superior to conventional repainting strategies in experiments, simulations and dose reconstructions. It may allow SBRT in the thorax and abdomen with proton PBS.

PTC17-0388: Clinical Commissioning of Rescanned Pencil Beam Scanning Treatments of Moving Targets

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This work was performed to commission the clinical procedure for the treatment of moving targets with pencil-beam scanning at PSI and involved 4D-planning and patient-specific verifications in both water and a dynamic anthropomorphic phantom.

3-field SFUD plans were optimized on the mid-ventilation phase extracted from a 4DCT dataset of each patient, with primary anatomical motion below 8 mm in superior-inferior direction. In a 4D-dose calculation study, 4-8 rescans were found to provide full and homogeneous target coverage. For dosimetric verification, each 8-times-rescanned field was measured at proximal, mid-SOBP and distal depth using a stationary 2D-chamber array and moving under different motion scenarios: nominal (8mm motion), fluctuating or scaled to exceed the clinical inclusion criteria ($>$10mm). Gamma score (GS) (3%/3mm) was 100% for all static measurements and $>$98.5% for all fields tested with nominal patient motion. Average GS reduced however to 97.8% (1SD=2.9%) in the presence of moderate motion fluctuations, and was not clinically acceptable for amplitudes $>$10mm (average GS=76.9%).

The whole clinical treatment workflow, including 3-DOF patient positioning based on image registration of the averaged 4DCT with a slow, pre-treatment in-room CT, was verified using an anthropomorphic breathing phantom and radiochromic films positioned at 2 planes in the tumour. Spatial displacement of measured dose distributions were 1.4mm (1SD=0.3mm) in the left-right direction and 1.5mm (1SD=0.0mm) in the cranio-caudal direction. Dose inhomogeneity in the CTV was $<$9%.

Our data suggest that rescanning can be safely applied clinically to mitigate motion with irregularities in moving-target treatments for amplitudes $\leq$ 8mm.

PTC17-0347: Evaluation of Motion Mitigation Using Abdominal Compression in the Clinical Implementation of Pencil Beam Scanning Proton Therapy of Liver Tumors

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This study presents a planning workflow that can be used for beam angle selection, as well as the evaluation of the efficacy of abdominal compression (AC) to mitigate motion, for liver tumor patients treated with pencil beam scanning proton therapy (PBSPT).

Four-dimensional computed tomography scans (4DCT) with and without AC were available from 10 liver tumor patients with fluoroscopy-proven motion reduction by AC. For each scan, the motion amplitudes and the motion-induced variation of water equivalent thickness (ΔWET) in each voxel of the target volume were evaluated during treatment planning. Optimal proton beam angles were selected after volume analysis of the respective beam-specific planning target volume (BSPTV). $M_{\perp 80}$ and ΔWET_{80} derived from the 80th percentiles of perpendicular motion amplitude ($M_{\perp}$) and ΔWET were compared with and without AC. 4D dynamic dose calculation was performed post plan to determine motion criteria for treatment.

AC resulted in reductions in mean Liver-GTV dose, $M_{\perp}$, ΔWET, and BSPTV volumes and improved dose degradation (ΔD_{95} and ΔD_1) within the CTV. For small motion ($M_{\perp 80} < 7$ mm and $\Delta WET_{80} < 5$ mm), motion mitigation was not needed. For moderate motion ($M_{\perp 80}$ 7-10 mm or ΔWET_{80} 5-7 mm), AC produced a modest improvement. For large motion ($M_{\perp 80} > 10$ mm or $\Delta WET_{80} > 7$ mm), AC and/or some other form of mitigation strategies were required.

A workflow for screening patients' motion characteristics and optimizing beam angle selection was established for PBSPT of liver tumors. Abdominal compression was found to be useful at mitigation of moderate and large motion.

PTC17-0267: Dosimetric Benefit of Fast Layer Switching in Treating Moving Target in Scanning Proton Therapy

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Purpose: Deterioration of dose distribution is common in plans delivered with scanning spots due to the interplay effect between moving tumors and spot sequences. Multiple solutions are available to mitigate the interplay effect with less attention to faster layer switching time (LST) due the technical hurdles in the older designs. With more spot scanning solutions available and stronger commitment from vendors to improve LST, a deeper understanding of the dosimetric benefit of fast LST for moving targets is needed.

Materials and Method: Plan comparison was conducted on a phantom and a clinical case between a developing synchrocyclotron system with in-gantry range shifter system for fast LST of 50ms and a popular isochronous system equipped cyclotron-end energy selection system with average LST of 1 second. In the phantom study, a spherical target of 8cm in diameter underwent sinusoidal motion of 12 cycles per minute with an amplitude of 1cm and 2cm respectively. In the clinical lung case, a plan was made on free-breathing helical scan. Dose was calculated on deformed images synchronized temporally with spot sequence. The deformation field was linearly interpolated from a b-spline image registration that was performed between the ends of inhalation and exhalation images. Spot settling time was set to 5ms.

Results: Our phantom study showed 1% and 7% reduction in coverage for respiratory motion of 1cm and 2cm with 50ms LST, significantly reduced from 4% and 17% with 1s LST. The clinical case showed similar result.

Conclusion: Our results demonstrate the improvements in delivery quality by using faster LST.

PTC17-0245: Advanced 4D IMPT Optimization for Multiple Moving Targets in Complex Geometry

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Purpose: Recent studies have shown the stereotactic body radiation treatment (SBRT) benefit for patients with advanced stage lung cancer (NSCLC). Intensity modulated particle therapy (IMPT) could better spare normal tissue, but achieving planning constraints for moving tumors in complex geometries is challenging. An algorithm was expanded for IMPT and compared to SBRT plans for patients with multiple targets of NSCLC.

Materials and Methods: A 4D optimization including all motion states was upgraded to include multiple targets, where each target is designated to specific field(s). Furthermore, to achieve stereotactic planning objectives, target and OAR weights plus objective doses were automatically adapted after each optimization until constraints were met. Rescanning was used as a motion mitigation technique and 4D doses were calculated for IMPT plans. The study included 8 patients with 24 lesions. Intended dose regimen was 24 Gy in 1 fraction, but lower fractionated doses had to be delivered in 3 cases due to OAR constraints.

Results: There was no significant difference in target coverage between SBRT and IMPT. However, the IMPT deposited 44% and 70% less dose to OARs for maximum point dose and dose to critical volume, respectively. An IMPT plan of single fraction could be created for a patient where SBRT was impossible.

Conclusions: An advanced 4D optimization algorithm was used to achieve superior IMPT treatment plans for stage IV NSCLC patients.

PTC17-0082: 4D Dose Computation in Pencil Beam Scanning Proton Therapy Has Been Clinically Implemented and Experimentally Verified

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Purpose: Pencil beam scanning proton therapy (PBS) enables conformal dose delivery to the target in three dimensions, but at the same time it is highly sensitive to setup and range uncertainties. Furthermore, the interplay between organ motion and beam motion may result in serious under- and overdosage for moving targets. In the current project, it will be investigated to which extent 4D robust planning mitigates motion-induced disturbances. For this purpose, a customized interplay effect routine was implemented in the treatment planning system RayStation. The experimental validation of the routine as well as preliminary results of a planning study are presented.

Materials and Methods: The interplay effect routine simulates the delivery of a scanned pencil beam to a moving target based on irradiation log files, 4D CTs and deformable image registrations. The experimental validation was done with the MatriXX PT detector and a dynamic phantom undergoing 4D CT acquisition, treatment planning and irradiation. The application of 4D-optimized PBS plans is studied for liver tumors with moderate motion amplitudes. Non-robust double scattering plans are used for comparison.

Results: The simulated interplay dose distribution is qualitatively consistent with the measured dose. For all experiments, the gamma index was above 96% which is within the tolerance range from 95% to 100% used for the patient quality assurance at WPE.

Conclusion: The interplay effect routine could be experimentally validated with a dynamic phantom measuring 2D dose distributions. It forms the basis for planning studies comparing robust and non-robust plans concerning over- and underdosage, dose homogeneity and sparing of normal tissue.

Nozzle Design, Beam Delivery and Dosimetry

PTC17-0281: Experimental Setup for First In-Phantom Measurements of Magnetic Field Effects on Dose Distributions of Proton Pencil Beams

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Purpose: To present an experimental measurement setup for MR-integrated proton therapy (MRiPT) dosimetry studies of magnetic field-induced dose distortion effects on slowing-down proton pencil beams in a tissue-equivalent phantom.

Materials and Methods: A 0.95 T NeFeB permanent dipole magnet was utilized to generate a transverse magnetic field over a $4\times20\times15$ cm^3 air gap. A PMMA slab phantom with Gafchromic EBT3 film was placed inside the air gap to measure planar dose distributions of 80-180 MeV proton pencil beams. Integrated depth-dose curves, beam trajectories, range and deflection of the Bragg peak were extracted from the films. A 3D finite-element model - developed to generate magnetic vector field data - was experimentally validated by Hall probe magnetometry. Repeated measurements of the magnetic field strength were performed to assess its stability during irradiation experiments.

Results: The modelled magnetic vector field data differed less than 2% from the measured data. Magnetic field-induced beam deflection was clearly observed from the planar dose distributions. Integrated depth-dose curves showed a similar form in comparison to measurements without magnetic field. Lateral displacement of the Bragg peak increased with energy from 1 to 10 mm for 80 and 180 MeV, respectively. Spot measurements of the magnetic field strength showed high reproducibility (σ=3 mT) and no effects of radiation-induced degradation.

Conclusion: For the first time, a measurement setup to study magnetic field-induced proton beam dose effects in a film phantom has been realized. The method is instrumental for building and validating Monte Carlo beam models for future MRiPT concepts.

PTC17-0184: Improving the Counting Statistics of Multi-Slit Prompt-Gamma Camera for Proton Beam Range Determination

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We have developed a multi-slit prompt-gamma camera for proton beam range determination in a patient. The developed camera, which has a field of view of 14.2cm with the measurement interval of 2mm, successfully determines the beam range based on the measured prompt-gamma distribution. However, if 10^8 protons are delivered to a beam spot, the camera can correctly determine the beam range for only ~20% of the cases for the most proton beam energies due to low counting statistics. In the present study, therefore, to address this low counting statistics, we suggest combing the prompt-gamma distributions measured from the different beam spots in the treatment volume, shifting the distributions in the beam direction to reflect the difference of the ranges. To test our idea, a Geant4 simulation was performed for spot scanning to generate a uniform spherical dose distribution of 2 Gy with a radius of 4cm at 8cm depth from a PMMA phantom surface. Then, we combined the prompt-gamma distributions and determined the range using the sigmoidal curve fitting on the combined distribution. Our simulation results show that the range can be measured within 1.4mm of error ($= 1\sigma$) if the total number of delivered protons for the combined distribution is equal to or greater than 3×10^8. Similar simulations were repeated for the different shape of treatment volumes and phantom geometries. The results show that the low counting statistics is no longer a problem, and that the camera with this approach can accurately determine the beam range in the patient.

PTC17-0164: High Resolution Silicon Detector Performance in Proton Beams at 1 T Magnetic Field: First Experimental Results

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Purpose: To report on experimental results of a 2-axis high spatial resolution silicon strip detector exposed to proton pencil beams in a 0.95 T transverse magnetic field. The magnetic field environment will be similar to that expected in future potential real-time MRI-guided proton therapy systems.

Materials and Methods: A C-shaped dipole permanent magnet device was utilized to generate a transverse 0.95 T magnetic field over a 4x20x15 cm volume. Inside this volume a 2-axis high resolution (0.2 mm pitch) silicon strip array detector was positioned parallel to the incident beam. Collimated proton beams (10 mm diameter) with an energy range 90-125 MeV were incident on the detector and the Bragg-peak was mapped out in in-line and cross-line profiles. For all experiments a corresponding Geant4 Monte Carlo simulation was performed.

Results: The shape and deflection of the Bragg-peak was successfully characterised at 0.2 mm resolution. The non-water equivalence of the silicon detector and phantom including air gaps acts to separate the Bragg-peak into multiple peaks depending on the proton paths taken. The deflection of the proton beams matched within +/- 0.5 mm of the Monte Carlo model.

Conclusion: For the first time, the performance of a high resolution silicon based detector has been succesfully tested with a proton pencil beam in a strong magnetic field. Silicon diode arrays are expected to be ideal in future efforts in MRI-guided proton therapy research as they offer high resolution real-time dosimetry.

PTC17-0161: Solid-State Microdosimetry of a Clinical, Spot-Scanning Proton Beam

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Purpose: Microdosimetry is a tool for assessing the microscopic patterns of energy deposition by radiation, which influences biological effect. Solid-state microdosimeters offer the capability of making measurements with high spatial resolution (10's μm). Such resolution is important in characterizing proton radiotherapy fields, particularly within the Bragg peak. We characterize a silicon-on-oxide microdosimeter (MicroPlus probe) in a clinical spot-scanning proton beam, by measuring lineal energy distributions and associated microdosimetric quantities.

Materials and Methods: The MicroPlus detector had a 3D silicon sensitive volume on top of silicon oxide, with active cross-sectional area of 250μm x 10μm and thickness of 10μm. Measurements were made in a water-equivalent phantom in water-equivalent depth (WED) increments of 0.25 mm along pristine Bragg peaks of energies 71.3 MeV and 159.9 MeV. We measured lineal energy distributions and computed the dose-mean lineal energy, yD. We used the clinical current (≈1nA) and had no detector pile-up.

Results: We find that yD increases with depth toward the distal Bragg peak, consistent with calculations and earlier measurements. For 71.3 MeV (R80=39.9 mm), we measured yD=1.9 keV/μm at WED=25.0 mm, and yD=12.2 keV/μm at WED=40.25 mm. For 159.9 MeV (R80=174.0 mm), yD=2.3 keV/μm at WED=50.0 mm, and yD=9.1 keV/μm at WED=177.0 mm.

Conclusion: We present the first microdosimetric measurements in a clinical scanning proton beam of small spot size and unmodified beam current. This device can now be used to characterize yD distributions of patient plans. The detector will be used for cell studies to correlate relative biological effectiveness with yD.

PTC17-0131: Ion Recombination in Scanned Light-Ion Beams Combining Boag's and Jaffé's Theory

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Purpose: To investigate ion recombination correction factors (k_s), which have to be applied to the response of plane-parallel ionisation chambers, in scanned light-ion beams.

Materials and Methods: Measurements were performed in four scanned light-ion beams (proton, helium, carbon, oxygen), using two plane-parallel ionisation chambers. Due to the high dose rates used with scanned beams and high LET-values, k_s results from a combination of volume and initial recombination. To separate both contributions, the saturation curve was measured at different dose per pulse values. Experimental results are compared to a model combining Jaffé's theory (initial recombination) and Boag's theory (volume recombination).

Results: Figures present the theoretical (lines) and the experimental (symbols) variation of k_s as a function of 1/V. Figure 1 shows results obtained in a pulsed PBS proton beam. Figure 2 shows results obtained in scanned carbon beams. Both figures show that initial recombination increases with LET and dominates at high voltages. Similar results are obtained for other beams.

Conclusion: Excellent agreement is found between experimental and theoretical k_s-values. Results confirm that k_s cannot be neglected. The solution to minimise k_s is to use the ionisation chamber at high voltage. However, one must be aware that charge multiplication may complicate the interpretation of the measurement. For the chamber tested, it was found that a voltage of 300 V can be used without further complication. As the initial recombination has a logarithmic variation as a function of 1/V, the two-voltage method is not applicable to these scanned beams.

PTC17-0129: Range Verification in Proton Therapy - on the Way to Clinical Translation

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The number of facilities offering proton therapy for curing tumors is growing steadily. Nevertheless, the benefit and precision of corresponding treatments is still limited by range uncertainties. In-vivo verification of the proton range would be of great value. We tackle this challenge by measuring time-resolved emission profiles of prompt gamma rays produced by the primary proton beam in interactions with nuclei of the tissue. After proving the principle, we intend to translate PGT in a clinically applicable technology.

Homogeneous and inhomogeneous targets have been exposed to proton pencil beams in the experimental cave, operated by OncoRay, as well as in the treatment room of the UniversitätsProtonenTherapie Dresden (UPTD). Single pencil beams of given energy, current, and duration, as well as complete 3D PBS treatment plans were delivered, respectively. The targets consisted of a hollow PMMA cylinder. The inner cavity could be partially or fully filled with cylindrical inserts of PMMA, bone surrogate, or other materials resembling tissue. Prompt gamma radiation was measured with 2" $CeBr_3$ scintillation detectors coupled to fast digital spectrometers.

The hardware has been extensively tested and characterized under clinical treatment conditions. Procedures for assigning list mode data to individual PBS spots, for correcting load effects, and for analyzing PGT spectra spot-by-spot have been developed. Cylindrical air cavities of 5mm depths could be identified in data sets collected with a single detector in 5 Gy PBS treatment plans. Range verification with 1 Gy PBS plans seems feasible if 4-8 detection units are applied.

PTC17-0111: 3D Range-Modulator for Proton Therapy: Development and Monte Carlo Simulations

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Purpose: Pencil beam scanning, though state-of-the art in particle therapy, hasn't yet established in the treatment of moving targets, due to the large number of different iso-energy layers and the associated long irradiation time. Treatment time of few seconds only can be achieved by using only one energy and a 3D range-modulator, thus making delivery of homogeneous dose to moving targets (e.g. lung cancer) more reliable.

Materials and Methods: A 3D range-modulator was developed for a spherical target of 5 cm diameter. The modulator was optimized using 151.77 MeV ^{1}H pristine Bragg-peak, corresponding to $\sim$ 15 g/cm^2 depth. It consists of pyramid-shaped pins with 4 mm^2 base area and different heights. The modulator was triangulated and manufactured in rapid prototyping technique. When irradiated, it creates a quasi-static irradiation field, tightly shaped around the target.

The resulting dose distribution and modulating effect were simulated using the FLUKA Monte Carlo package. Two additional user routines were implemented: one to handle the complex geometry contour of the modulator and a second one for intensity modulated scanning.

Results: The principle of the 3D range-modulator and the corresponding simulation results are shown in Fig. 1.

Conclusion: FLUKA simulations show a flat spread-out Bragg-peak and homogeneous 3D dose distribution conformed not only to the distal, but also to the proximal edge of the target. Due to the very short irradiation times, the 3D range-modulator can be an alternative to consider when treating small to medium sized moving tumours.

PTC17-0106: Irradiation System of the Stereotactic Radiosurgery for Carbon Particle Beam

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The objective of this research is to develop the stereotactic radiosurgery for Carbon beam to treat the small intracranial lesion that we call Carbon-knife. Gunma University has developed a 2D-scanning using RF-knock out method to perform carbon-knife system. The field sizes were generated with a 2x2cm^2 field size and a scanner step of 2mm

The carbon energy of 170 to 290 MeV/u in 20 MeV/u steps corresponding 5 cm and 15 cm range in water was used. For longitudinally spreading the beam, the ridge filter with 5mm, 7.5mm, and 10mm SOBP, which is included the fluence attenuation factor have been prepared. The 3 sizes of the collimator, which is used to reduce the dose to surrounding normal tissue, were 2x2mm^2, 3x3mm^2, and 10x10mm^2.

PDD and beam profile data were checked using 170 MeV/u and 290 MeV/u. The lateral penumbra is defined at the point 80% to 20%of the maximum dose. The penumbras were measured at eight different depths according to the PDD results.

PDD with 5, 7.5 and 10mm SOBP were measured by an advance Markus ionization chamber and compared with calculated depth dose distributions. The beam profiles were measured by a diode dosimeter (PR type 60020). The results of the lateral penumbra are less than 2mm in every collimator size.

Basic data of the carbon knife system, depth dose and lateral penumbra size, were obtained at Gunma University. The suitable ridge filter and collimator will be selected for therapeutic usage depending on the target volume and tumor site.

PTC17-0088: Measuring Hadrontherapy Microdosimetric Distributions at Nominal Fluence Rate

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In developed countries, the use of protons and hadrons (heavy ions) to treat tumours using radiation therapy is increasing because of the higher radio-biological efficiency (RBE) compared to traditional therapies (electrons and X-Rays). The knowledge of the energy deposition along the particle tracks at submicrometric scales is paramount to the characterization of the RBE. To accomplish this there are several alternatives, as using gaseous TEPC detectors, but alternatively devices based on silicon can be used. Silicon detectors have several advantages over the TEPC detectors, such as a smaller volume and easier operation.

The present work shows the latest version of a 3D ultrathin silicon micro-dosimeter array developed by the IMB-CNM (Spain). This matrix consists of 11×11 cylindrical sensitive cells with individual readout etched within the silicon substrate with an individual cell diameter of 15 micrometres and a thickness of 5 micrometres. The detectors have been produced over a silicon substrate of 300 micrometres or used in its thinned version, being supported by a silicon frame. Several successful tests were performed in the clinical facilities of CNAO (Pavia, Italy), employing a pencil beam nominal therapeutic fluence rate for the first time. Microdosimetric spectra of lineal energy were measured on a 12C beam in different depths of Lucite up to the Bragg peak. The results were compared with Monte Carlo simulations calculated using FLUKA, showing an excellent agreement between the experimental and simulated microdosimetric distributions.

Treatment Planning

PTC17-0516: Comparison of Single-Field and Robust Multi-Field IMPT Plans for Oropharynx Carcinoma by an Enhanced Method of Robustness Analysis

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Purpose: Presentation of an enhanced robustness analysis and its application on single-field (SFO) and robust multi-field optimized (rMFO) plans for intensity modulated proton therapy (IMPT).

Materials and Methods: rMFO IMPT plans were optimized (Eclipse v13.7, Varian, Palo Alto, CA) for 11 oropharynx carcinoma patients receiving postoperative radiotherapy with SFO IMPT using simultaneous integrated boost prescription. Expected mean dose per voxel is calculated for minimal, 0% and maximal range uncertainty (RU), considering 19 setup error (SE) scenarios and their likelihood of occurrence. Voxel-wise boundary dose distributions are created from all 57 scenarios including systematic RU and random SE while also taking into account the average effect of fractionation to approximate realistic worst cases for the total treatment course. Dose error distributions and under- and overdosage of target/organ-specific metrics are derived from these boundary doses.

Results: Nominal rMFO plans show improved CTV coverage and homogeneity with simultaneous reduction of the average mean dose to the constrictor muscles, larynx and ipsilateral middle ear by 5.6Gy(RBE), 2.0Gy(RBE) and 3.9Gy(RBE), respectively. The comparison of SFO and rMFO boundary doses reveals slightly larger differences for these organs, and significantly lower brainstem maximum and ipsilateral parotid mean dose in rMFO plans. Many dose error metrics are significantly superior for rMFO plans.

Conclusion: Better CTV coverage and OAR dose sparing of nominal plans is preserved by rMFO compared to SFO plans under considerations of SE and RU. DVH bands and dose metrics from the boundary dose distributions will help to judge plan robustness in clinical routine.

PTC17-0500: Concept of an Advanced Treatment Planning for Ocular Proton Therapy

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Purpose: Towards an automated treatment planning process for ocular proton therapy.

Materials and Methods: A patient specific eye model (tumor and organs at risk (OaR)) is first exported from EyePlan into our standalone application. Using the eye globe, anterior part of the eye (cornea), macula and optic disc as critical organs, cumulative DVHs are created by calculating the doses on an individual grid (20*20*20 points) for each OaR and each possible eye position. To relatively score the ‘quality’ of each eye position, dose-volume criteria for each OaR are summed over the valid criteria of all OaR for each eye position and presented to the user as a colour coded map.

Result: The dose calculation has been found to be equivalent to that of EyePlan. For ten patients, all clinically planned using EyePlan, DVHs of the treatment position were extracted and compared to the DVHs calculated by our standalone application. Differences between the two systems had a standard deviation of +/-0.67%, whilst the discrepancies never exceeded -2.2%, +1.7%. Increasing the resolution of the grid increases calculation accuracy.

Instead of testing one eye position at a time, this tool provides a quantifiable overview of the whole treatment phase space. It substantially reduces planning time and can help automate the treatment planning process for the treatment of ocular tumours. In addition, adaption of dose-volume criteria enables the planner to take into account trade-offs between all OaR and find the best possible solution.

PTC17-0296: What Is Needed to Demonstrate the Benefit of Dual-Energy CT for Particle Treatment Planning?

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Purpose: To thoroughly understand and quantify the benefit of dual-energy CT (DECT) for the reduction of range uncertainty in particle treatment planning.

Materials and Methods: In a multi-step procedure, DECT-based direct prediction of stopping-power ratios (SPRs) was improved in accuracy, robustness and clinical applicability by optimizing CT scan protocols, as well as post-reconstruction voxelwise SPR calculation algorithms. Subsequently, it was verified by three independent, yet complementary, studies in comparison to the current clinical standard (single-energy CT, SECT): (A) a relative comparison in patient cases; two absolute comparisons in (B) a controlled experimental setting measuring photon and ion absorption in animal tissues and tissue base components; and in (C) an inhomogeneous head phantom providing a well-established ground truth.

Results: For a large collective of proton therapy patients (A), substantial intra- and inter-patient variability in CT-number-to-SPR-conversion as well as relative range differences of about 1.5-2.5% between SECT- and DECT-based treatment plans were observed. Both reveal the relevance of accurate CT-based SPR prediction and the potential for improvement. While naturally missing in patient studies, a reliable ground truth was provided in (B) and (C) to allow for absolute evaluations of SPR accuracy. The DECT method hereby proved capable to correctly predict SPR of homogenized animal tissues, tissue base components and the tissue substitutes in the anthropomorphic head phantom within measurement uncertainty.

Conclusion: Only with the all-encompassing combination of theoretical considerations, lab experiments and the analysis of patient data, we are able to demonstrate clinically relevant reduction of range uncertainty with DECT-based treatment planning.

PTC17-0274: How Much Can Range Accuracy in Proton Therapy Be Improved Through Patient Specific Optimization of the HU-RSP Conversion Curve?

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When treatment planning in ion beam therapy is performed based on X-ray CT data, the Hounsfield Units (HU) are approximately converted to relative stopping power (RSP). The range uncertainties associated with the conversion process require additional safety margins around the contoured treatment volume. Meanwhile, proton imaging provides a direct probe of RSP. A patient specific optimization of the HU- RSP conversion curve by comparing proton radiographic images with digitally reconstructed radiographies (DRR) has previously been suggested. In this contribution, we investigate the influence of several factors on the accuracy of this optimization, i.e., the projection model for the DRR, the co-registration of proton radiography and X-ray CT, and the choice of approximation intervals of the HU- RSP curve. For this purpose, experimental proton imaging data is inadequate because the true RSP values are not known for anthropomorphic phantoms of realistic complexity. Instead, we generate ground truth data through experimentally validated Monte Carlo (MC) simulations. To assess the expected therapeutical gain and the influence of the aforementioned factors thereon, we (re-)calculate treatment plans based on optimized and non-optimized X-ray CT (in RSP). We compare the predicted dose maps with the one obtained from a MC simulation of the treatment, with a special regard to edges near organs at risk. We will finally quantify by how much range accuracy can be improved through patient specific optimization of the HU-RSP conversion curve.

PTC17-0204: Optimization of Energy Layers for Delivery Speed and Plan Robustness

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Purpose: The number of energy layers and the step size in-between are fundamental parameters in proton treatment planning. How they are chosen will influence delivery speed, target coverage and plan robustness. For lung cancer patients where gating and rescanning are used, the balance between these parameters is essential.

Materials and Methods: We have implemented three different energy layer strategies in the treatment planning system Hyperion; predefined constant steps, predefined exponential energy dependent steps and finally an adaptive strategy, where the optimization problem is regularized by a group sparsity penalty on the spot weights with a subsequent layer exclusion. The three strategies are hereafter used in treatment plans with three fields and identical constraints. They are created on the mid ventilation phase of a lung case to simulate gating. A minimum dose to the target is ensured, which implies the plan quality is reflected in the maximum target dose and the outcome of the robustness evaluation.

Results: The energy layer pattern for the adaptive strategy is shown in figure 1. The target coverage and the results from the robustness evaluation are shown in figure 2. The largest differences in robustness are seen in the D02 parameter.

Conclusion: The number of energy layers can be reduced by $>$ 50% while maintaining an acceptable robustness and target coverage. The most robust strategy is the exponential strategy. This could be explained by the closely spaced layers at high energies, which are also seen in the adaptive strategy to some extend.

PTC17-0152: Impact of Metal Artifacts on Proton Therapy Treatment Planning Accuracy

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Purpose: To evaluate for proton therapy treatment planning the feasibility of two commercial metal artifact reduction (MAR) algorithms in CT-imaging.

Materials and Methods: A head phantom with removable dental fillings and a body phantom with a removable hip prosthesis were scanned to evaluate O-MAR (Philips) and iMAR (Siemens). Reference images (scans without metal) were acquired and subtracted from the uncorrected (no MAR) and MAR-images. CT number-differences were mapped to differences in stopping power ratios to water. In addition, proton treatment plans for a parotid, tonsil and prostate-target were optimized based on uncorrected and MAR images and recalculated on reference images. Beams were arranged to not traverse metal, enabling evaluation of metal artifact impact on target coverage.

Results: MAR algorithms reduced the most extreme dental filling artifacts, but residual artifacts still remained. iMAR reduced hip prosthesis artifacts to large extent, while considerable artifacts still were present with O-MAR. For parotid and tonsil-plans, $D_{98\%}$ to PTV was nearly intact in the reference recalculations for both uncorrected and MAR-based plans, with maximum-difference $<0.3\%$. For uncorrected prostate plans, $D_{98\%}$ decreased more than 4% in the reference recalculation. For the iMAR prostate plan, $D_{98\%}$ was almost identical in the reference recalculation (97.5% versus 97.4%). A slight $D_{98\%}$-decrease was seen in the reference for the O-MAR based plan (96.8% versus 97.5%).

Conclusion: Hip prosthesis artifacts reduced target coverage accuracy, but it was substantially improved with MAR algorithms. Dental filling artifacts were moderately reduced with MAR, but did not substantially affect target coverage.

PTC17-0085: Robust Intensity-Modulated Proton Therapy to Reduce High Linear Energy Transfer Exposure in Organs at Risk

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Purpose: We propose a robust intensity-modulated proton therapy (IMPT) planning model that simultaneously considers proton range and patient setup uncertainties and reduces high linear energy transfer (LET) exposure in organs at risk (OARs) to minimize high relative biological effectiveness (RBE) dose in OARs.

Materials and Method: We retrospectively generated plans for 3 patients with prostate, head and neck and lung cancer. The "worst-case robust optimization" model was applied. One additional term related to the "biological dose (*BD*)" of OARs was added in the objective function. The *BD* is defined as the product of physical dose and dose-averaged LET and captures the increased risk to OARs due to high LET. The model first compares the worst-case doses among all scenarios with the prescription dose and then penalizes hot and cold spots within tumors and penalizes hot spots and areas of high *BD* within OARs. Our new model was compared with the regular robust planning model without considering the influence of LET.

Results: For the 3 cases included in this study, our model outperformed the regular robust model in terms of avoiding high *BD* regions within OARs. At the same time, our method achieved physical dose distributions and plan robustness of tumors almost as good as those from the regular robust model.

Conclusion: Our model can reduce the risk of toxicity from high RBE (high LET) dose deposition within the OARs without sacrificing plan quality and robustness.

PTC17-0084: Considering Bragg Curve Degradation Due to Lung-Equivalent Material in Monte Carlo Codes by Applying a Density Modulation

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Purpose: Sub-millimetre-sized heterogeneities like lung tissue cause Bragg peak degradation. If not considered in treatment planning this can significantly influence the dose distribution in lung cancer patients. We are capable of considering Bragg Peak degradation in Monte Carlos codes and hence MC-based treatment-planning systems by applying a density modulation within the voxels associated with the lung.

Materials and Methods: The treatment plan of a hypothetical PTV in water downstream from lung tissue was optimised based on realistic CT data where the lung's fine structure is not resolved hence an average dose is predicted in each voxel. This plan was then simulated with the Monte Carlo code TOPAS. In a second simulation the density in each voxel was modulated, which corresponds to the situation of irradiating a real patient where the heterogenous lung tissue leads to a Bragg peak degradation.

Results: In Figure 1 the 2d dose distributions for both scenarios. The PTV is marked by the rectangle. In the first case the dose is homogeneously distributed within the PTV. In the second realistic scenario the distal fall-off is blurred resulting in an underdose of the PTV and an overdose of the distal healthy tissue. In Figure 2 the corresponding dose-volume-histogram emphasising the underdosage of the PTV when the Bragg peak degradation is not considered in treatment planning.

Conclusion: We are capable of considering Bragg peak degradation due to lung-equivalent materials in Monte Carlos codes by applying a density distribution. We can hence consider and analyse the effects of this degradation in treatment planning.

PTC17-0016: A Novel Robust, Delivery-Efficient and Continuous Spot-Scanning Proton Arc(SPArc) Therapy Is to Improve the Dosimetric Outcome in Treating Prostate Cancer

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Purpose: The recent publication of the first Spot-Scanning Proton Arc (SPArc) therapy platform demonstrated the potential to further improve the proton dosimetric outcome in certain disease sites. This is the first study to exploit the dosimetric benefits and feasibility of using SPArc in treating early stage prostate cancer.

Materials and Methods: Nine early stage prostate cancer patients were included in the study. Bilateral robust optimized Intensity Modulated Proton Therapy(ro-IMPT) plan and SPArc plans were created using the same robust optimization parameters with $\pm$3.5% range and $\pm$5mm in x,y,z directions. Plan quality and total estimated delivery time were compared between ro-IMPT and SPArc plan groups. Root-mean-square Volume Histogram(RVH) is used to evaluate the plan robustness. Total delivery time was estimated based on a full gantry room with 1 RPM , 2ms spot switching time, and different energy-layer-switching-time(ELST) (0.1s - 5s).

Results: With the similar target coverage and robustness, the dose to both rectum and bladder was significantly reduced in SPArc plans($p<0.05$). Compared to ro-IMPT, SPArc reduced maximum skin dose by an average of 13.50Gy[RBE]. Furthermore, SPArc resulted in decreasing the body integral dose of about 11%($p=0.003$). Plan robustness to rectum, bladder, femoral heads are significantly improved correspondingly. More importantly, SPArc could finish delivering a plan within 5mins when ELST is 1 second and it has a comparable delivery time to ro-IMPT when the ELST is close to 0.1s($p=0.656$).

Conclusion: SPArc has been shown to be clinically valuable and feasible while significantly improving the dosimetric outcome and plan robustness in prostate cancer radiotherapy.

Dose Calculation and Optimization

PTC17-0302: Nonlinear Robust Optimization Methods for 4D Treatment Planning in Carbon Ion Therapy

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Purpose: We introduced robust optimization into non-linear biological optimization of GSI's TRiP4D to avoid internal IMPT dose inhomogeneities. Here we present a conformal robust 4D optimization delivering a homogeneous dose to each motion phase.

Materials and Methods: The implemented worst case scenario method currently considers 9 different scenarios in the optimization process (nominal scenario, ±3.5 % range shifts and ±5 mm target shifts in 6 directions). In every iteration step LEM-based RBE-weighted doses are calculated for all scenarios from the current set of beam fluences respecting fragment spectra and LET. Within the conformal 4D optimization approach robust IMPT is compared to conventional IMPT with 5 mm isotropic margins regarding 4D dose distributions for different uncertainties.

Results: Robust IMPT was tested in a patient case with a lung tumor in close proximity to heart, a motion amplitude $>$ 2 cm. Optimized to a target dose of 9.4 GyE, heart maximal point dose could be reduced from 10.51±0.56 GyE to 8,57±0.77 GyE averaged over all scenarios by slightly decreasing V95 from 87.6±10.6 % to 85.8±4.8 %. The steeper falloff and smaller spread in the robust DVHs could enable space for a potentially higher target dose.

Conclusion: An initial patient simulation shows the feasibility and the importance for robust (4D) optimization methods for moving targets in carbon ion therapy. A further extension of the algorithm for a full 4D robust optimization where the impact of all CT phases is considered in every iteration step will follow.

PTC17-0279: Open Source Proton Treatment Planning in 3D Slicer: Status Update

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Purpose: We describe the current status of open-source, proton-beam treatment planning on 3D Slicer, including design, implementation, and long-term potential.

Materials and Methods: Modern radiotherapy treatment planning software comprises such software components as beam specification, dose calculation, plan optimization, plan visualization, and plan reporting. Interactive components, such as visualization and beam specifications, are implemented in the SlicerRT extensions of 3D Slicer, a widely used open-source platform for medical image computing. Dose calculation based on the Kanematsu-Gottschalk pencil-beam scattering model is implemented in Plastimatch for both passive scattered and scanned beams. Treatment plan optimization is implemented in opt4D, which is capable of optimizing physical and biological doses with both soft and hard objective constraints.

Results: At the time of abstract submission, an implementation of the open source TPS is available in the experimental build of SlicerRT (slicerrt.github.io). This implementation is capable of 3D forward planning and uniform scanned beams. Treatment plan optimization with opt4D requires a separate download. Efforts to integrate as a single download is ongoing.

Conclusion: Modern radiotherapy treatment planning using a fully open-source software is feasible, and supports advanced research in proton-beam therapy.

PTC17-0207: Simultaneous Optimization of RBE-Weighted Dose and Ionization Clustering in Treatment Planing with Carbon Ions

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Purpose: Different carbon ion treatment plans can satisfy the requirements on target coverage and sparing of healthy tissues while differing with respect to quantities of interest other than RBE-weighted dose, e.g., LET or ionization clustering. We hypothesize that RBE-weighted dose and clustering effects [1] can be concurrently optimized to obtain homogeneity of these different endpoints in the target volume.

Materials and Methods: The treatment planning system matRad [2] was extended to compute ionization clustering and account for simultaneous optimization of RBE-weighted dose and ionization clustering of carbon IMRT. A base data of pencil beams including ionization clustering profiles was generated with the Monte Carlo method using TOPAS [3]. In order to test our hypothesis, treatment plans were generated for a 40x40x40 mm^3 PTV, centered in a 168x168x168 mm^3 water phantom, and receiving 3 Gy-RBE using different beam orientations and optimized w.r.t. RBE-weighted dose and ionization clustering.

Results: DVHs and volume histograms of large ionization clusters (more than 3 ionizations within 3.4 nm distance) were obtained with two orthogonal beams optimized w.r.t. i) RBE-weighted dose only (solid lines), and ii) RBE-weighted dose and ionization clustering (dashed lines). Similar results were obtained with other beam configurations.

Conclusion: Ionization clustering and biological dose uniformity can be simultaneously optimized without impairing target coverage.

References: (1) M Casighari, RW Schulte 2015. Comp Math Methods in Medicine 908971:1-908971:13. (2) matRad - An open source multi-modality radiation treatment planning system. http://www.matrad.org. (3) J Perl et al. 2012. Med Phys 39(11): 6818-37.

PTC17-0169: Validation and Clinical Implementation of a Full Monte Carlo Code for Scanned Proton Pencil Beams

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We present a universal method to model a proton PBS dedicated nozzle by using acceptance and commissioning measurements, together with a full Monte Carlo (MC) code (Topas/Geant4), to address both the halo inherent from the nozzle as well as a simplified implementation of a range shifter. A two Gaussian source spot profile model was implemented to better address the halo due to interaction of protons with components in the nozzle. The phase space parameters and protons per MU were extracted and tuned without simulating any components of the nozzle by comparing Topas simulation with a series of commissioning measurements using scintillation screen/CCD camera detector and ionization chambers. The range shifter was simulated as an independent object. The beam model was validated by comprehensive measurements of the size of single spots, field size factors (FSF) and three dimensional dose distributions of Spread Out Bragg Peaks (SOBPs) both without and with the range shifter. Figure 1 shows FSF along beam path in air and in water after the range shifter for energies of 115 and 225 MeV. The excellent agreement between a TOPAS and measurement reflects high accuracy of Topas in halo's modeling. To demonstrate the application in clinical treatment planning, the source model was directly implemented into a second fast, PBS dedicated MC code, MCsquare. Figure 2 shows a representative head-and-neck case calculated using TOPAS, MCsquare and a commercial treatment planning system (Eclipse 13.7). In conclusion, two different MC codes have been implemented with universal commissioning method for treatment quality assurance.

PTC17-0151: Robust Optimization of Intensity-Modulated Proton Therapy Based on Per-Voxel Dose Interval Distributions

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Purpose: Traditional voxel-wise worst-case robust optimization can render IMPT plans insensitive to uncertainties. However, treatment planners cannot explicitly control the balance between plan robustness and plan quality. In many cases, physicians may wish to control the balance based on clinical priorities. We propose a new way of robust optimization based on per-voxel dose interval distributions to explicitly control the tradeoffs between robustness and plan optimality.

Materials and Methods: Multiple dose distributions are computed during the optimization: each corresponding to a different uncertainty scenario. The dose interval (DI = maximum dose – minimum dose) for each voxel is used to create DI-volume histogram (DIVH) for each structure. Dose volume histogram band widths and the areas under the DIVH curves are used to quantify plan robustness. The desired robustness may be specified in terms of a DI-volume constraint (DIVC) on the targets and incorporated as terms in the objective function. Penalty parameters for DIVCs may be adjusted to explicitly control the tradeoff between robustness and plan optimality. We tested our method on two lung cases and one H&N case. Results are compared to the traditional voxel-wise worst-case robust optimization.

Results: Our new method can achieve comparable plan quality with superior robustness. By relaxing the DIVCs, it is possible to improve plan quality.

Conclusion: The DIVC-based robust optimization is an effective method, which can not only compete with the traditional voxel-wise worst-case robust optimization, but also allows radiation oncologists to explicitly control the balance between plan quality and plan robustness.

PTC17-0074: A New Method to Investigate the Fragmentation of Carbon Ions: First Results for Water and Non-Water Materials

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Purpose: The experimental setups currently used to investigate ion fragmentation are based on ToF measurements, and therefore they are several meters large. We developed a new method to analyse ions fragmentation in different materials. The new small experimental setup can be easily implemented in clinical facilities.

Materials and Methods: Tissue surrogates (lung, adipose, inner and cortical bone) and water targets, which in pairs have the same water equivalent thickness (WET), were used. The targets were irradiated with carbon ion beams at the HIT center in Heidelberg. Single particle position, arrival time, and energy loss were measured with the semiconductor Timepix detectors [Llopart et al. NIM A581, 2007]. Three detectors behind the targets allowed particle species identification and particle tracking. For comparison, Monte Carlo simulations of the experiments were performed using FLUKA-2011.2.

Results: Residual number of carbon ions, secondary fragments and lateral particle distributions were measured behind each target. In general, the experimental results were consistent between adipose / inner bone surrogates in comparison to water targets with the same WET. Greater differences were measured in the case of lung and cortical bone with respect to the corresponding water targets. Significant differences were observed between the experiments and the simulations.

Conclusion: Despite the same WET, different ion spectra were measured behind tissue and water targets. This research aims to improve the accuracy in the prediction of the secondary radiation in non-water materials.

Image Guidance and Adaptive Therapy

PTC17-0332: Proton Dose Calculations on a Priori Scatter Corrected Cone-Beam CTs Acquired on Photon vs Proton Therapy Gantries

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Background: Cone-beam (CB) CT imaging may enable image/dose-guided proton therapy, but is challenged by image artefacts. The aim of this study was to explore the use of an *a priori* scatter correction algorithm on CBCT projections acquired on photon vs. proton therapy gantries and to investigate consequences for CBCT-based proton dose calculations.

Materials and Methods: The *a priori* scatter correction algorithm used a plan CT (pCT) and raw CB projections. The projections were acquired with an On-Board Imager of both a Varian photon therapy Clinac and a proton therapy ProBeam system and were first reconstructed conventionally (rawCBCT). Manual, rigid and deformable registrations of the pCT were then forward projected onto the same angles as the raw CB projections. The difference between the two projections sets were, after smoothing, subtracted from the raw projections to obtain the scatter corrected CBCT. For evaluation, water equivalent path length (WEPL) maps were calculated on different reconstructions of the data sets (CB projections and pCT) of an Alderson phantom for the Clinac and of the CatPhan phantom for both systems.

Results: For the Alderson phantom the scatter correction resulted in sub-mm mean WEPL difference from the rigid registration of the pCT. For the CatPhan phantom the CBCT on the photon gantry showed smaller WEPL differences than on the proton gantry.

Conclusion: We have shown that an a priori scatter correction algorithm for CB projections improves CBCT image quality on both photon- and proton therapy gantries, potentially opening for CBCT-based image/dose-guided proton therapy.

PTC17-0288: Patient Positioning and Motion Management Using Optical Surface Scanning – an End-To-End Study within the Swedish National Proton Project

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Purpose: Within the Swedish national proton project, patients selected for proton therapy are CT-scanned and treatment planned at their home center followed by treatment at the proton center, Skandionkliniken. In order to assess respiratory motion management, a three-camera optical surface scanning system (OS) has recently been installed.

The aims of this study were I) to evaluate the accuracy of the OS system in this world-wide first proton installation, and II) to carry out a multicentre end-to-end test of DIBH gated spot-scanning using real patient breathing data reproduced by a breathing-simulated motion phantom.

Materials and Methods: To study the accuracy, an anatomical head phantom (HP) was used and couch shifts of $\pm$5 mm and $\pm 3^\circ$ in rotation, roll and pitch, respectively, were carried out. The HP was positioned with the OS system for a shallow and a deep target and the position was then verified by kV/kV imaging.

For the end-to-end test, the moving phantom was scanned in DIBH at CT_{home}, $CT_{Skandion}$ and gated kV-kV imaging was carried out in DIBH at the treatment gantry. The reproducibility in position of the internal structure was evaluated.

Results: The accuracy of the surface based setup was within 0.7$\pm$0.4mm in all directions for the shallow and deep iso-center positions, respectively. The positioning accuracy for the moving target was within -0.8$\pm$0.7mm at the treatment gantry.

Conclusion: This multicentre end-to-end study showed that the unique proton adapted OS three-camera setting can assure patient setup as well as reproducibility during DIBH treatment.

PTC17-0240: First Clinical Prompt Gamma Imaging for in vivo Range Verification in Pencil Beam Scanning Proton Therapy

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Purpose: To report the first clinical results and value assessment of prompt gamma (PG) imaging for *in vivo* proton range verification in pencil beam scanning (PBS) mode.

Materials and Methods: A standalone, trolley-mounted, prototype PG camera, utilizing a knife-edge slit collimator design was used to record the PG signal emitted during proton irradiation for a brain cancer patient. The camera was aligned perpendicular to the central beam axis using an embedded laser. The recorded PG depth detection profiles of individual pencil beam spots were compared to the expected profiles simulated from the treatment plan.

Results: In 6 treatment fractions recorded over three weeks, the mean range shifts aggregated over all spots in 9 energy layers were 0.7 ± 1.3 mm for the lateral field, 3.2 ± 0.7 mm for the right-superior-oblique field and 1.1 ± 0.9 mm for the vertex field. These shifts were smaller than the range uncertainty margins applied to the target during planning.

Conclusion: This study demonstrates the feasibility and illustrates the distinctive benefits of prompt gamma imaging for the PBS treatment mode. Accuracy in range verification was found in this first clinical case to be better than the range uncertainty margin applied in the treatment plan. These first results lay the foundation for additional work towards tighter integration of the system for in vivo proton range verification and quantification of range uncertainties.

PTC17-0235: Development of a Clinical System for Proton Range Verification through Prompt Gamma-Ray Spectroscopy

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We will present the latest status of the development of a clinical prototype system for *in vivo* proton range verification at the Massachusetts General Hospital. The system performs spectroscopic measurements of prompt gamma-rays that are emitted during the decay of excited recoil nuclei from proton-nuclear interactions with the patient's tissue. By resolving the gamma-rays in dimensions of energy and time, gamma-rays from different nuclear reaction channels are separated and proton-induced events can be distinguished from the neutron-induced background. This quantitative measurement of the nuclear reactions enables real-time verification of the absolute proton range.

Our prototype detector, which consists of a tungsten collimator and 8 large lanthanum(III) bromide scintillation crystals, has recently been completed. We have also finalized the readout electronics and the data acquisition system, which are now fully integrated with the clinical beam delivery systems. A motorized positioning device provides 3-dimensional translation and rotation of the detector in the treatment room.

To verify the range of clinical proton fields, a fast workflow has been developed. GPU accelerated simulations are used to calculate expected gamma-ray emissions from different reactions as a function of the range of each individual proton pencil-beam. These simulations are based on experimentally determined cross sections. By comparing the calculations with the measurements, the absolute ranges of the beams are determined.

We are currently preparing the first-in-human study of the system. It will be tested during pencil-beam treatments of patients with intracranial tumors.

PTC17-0229: BioXmark® Remains Chemically Stable Following Normofractionated and Single-Fraction High-Dose Proton Beam Irradiation

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Purpose: Recently, a liquid carbohydrate based fiducial marker (BioXmark®) has been introduced with minimal dose perturbation (relative stopping power = 1.164) and visibility properties suitable for use in image-guided proton therapy (IGPT). In this study we investigated the chemical stability of the marker for use in both normofractionated and single fraction irradiation to a high dose.

Materials and Methods: A QA dosimetry phantom was modified to simultaneously accommodate four cylindrical polymethylmethacrylate (PMMA) inserts. In total, ten identical (PMMA) inserts were custom-made: BioXmark® markers were added at the bottom of the inserts, water was added on top of the markers and they were sealed. Using the modified QA dosimetry phantom, the PMMA inserts were placed sideways into the proton irradiation field. Four markers (Group A) were irradiated during daily QA to an accumulated dose of 67.4 Gy in 43 fractions, four other markers (Group B) were irradiated with a single dose of 155.4 Gy, and two non-irradiated inserts served as control markers. High-performance liquid chromatography (HPLC), electrospray ionization mass spectrometry (ESI-MS), thin-layer chromatography (TLC) were used for chemical assessment of the irradiated BioXmark® markers and the overlying aqueous phase.

Results: There were no visually apparent changes in any of the inserts. HPLC, TLC and ESI-MS analysis of the markers and the aqueous phase did not indicate chemical degradation in any of the groups.

Conclusion: The BioXmark®marker showed no chemical degradation after exposure to high-dose normofractionated and single-dose proton beam irradiation and may serve as a good alternative to solid fiducial markers currently used for IGPT.

PTC17-0206: X-Ray Flat Panel as Single Detector for Proton Imaging with Scanned Proton Beams

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Single detector proton imaging using energy resolved dose measurement (ERDM) has been demonstrated to be feasible with pencil beam scanning (PBS) proton therapy.In order to demonstrate this technique in an optimized workflow, we tested the method using an X-ray flat panel detector.

A Varian Flat Panel detector, is calibrated for use with ERDM for proton imaging.The efficiency and reproducibility of the flat panel is investigated for proton beam with different spot weights between 0.0001MU and 0.01MU, with 1MU=3nC.After determining the optimal proton spot weight for imaging, the detector is used to record a dose map delivered by a PBS imaging field.The imaging field was used to image four configurations: (i) a wedge water phantom for calibration;(ii) a homogeneous stairs-like phantom;(iii) a CIRS phantom with multiple tissue equivalent inserts and (iv) a head phantom.

The sensitivity benchmarking tests of the detector indicated that 0.001MU is the most appropriate proton spot weight for imaging without flat panel saturation, yet with acceptable reproducibility.The WEPL accuracy obtained from homogeneous targets (Config.ii) was better than 3mm.The relative stopping power derived from the imaging of the CIRS phantom was better than 3%.The quality of the WEPL image of the head phantom and the Multi-Coulomb Scattering image derived from the range mixing signal, show satisfactory anatomic details with promising potential for clinical applications.

The preliminary results for using an X-ray flat panel for proton imaging in PBS mode are encouraging.Additional optimization of the imaging set-up and workflow will be necessary before any integration into an image guided proton therapy workflows.

Acceptance, Commissioning, and Quality Assurance

PTC17-0518: Quality Assurance and Human Error: A New Approach towards Human Reliability Analysis (HRA) in Radiotherapy Performed at CPT/PSI

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Purpose: QA and safety measures traditionally ensure patient safety and quality in radiotherapy. Nevertheless, failures that occur are usually not related to RT system malfunctions but rather to human interactions and failures and are of critical importance. We have therefore developed a Human Reliability Analysis (HRA) method to analyze and quantify potential human failures in proton therapy at Paul Scherrer Institute.

Materials and Method: HRA consists of three phases: (1) qualitative: to identify critical tasks and associated performance conditions, (2) quantitative: to design a quantification framework and obtain failure probabilities, and (3) application: to optimize quality of patient care by analytical scenario prioritization and safety improvement evaluation. Using retrospective analyses of incident databases, referencing existing HRA methods, and prospective techniques like human performance models and Hierarchical Task Analysis (derived from talk-throughs and observations at CPT) we developed taxonomies of critical tasks and conditioning factors.

Results: 6 generic tasks types (GTTs), supported by 40 example tasks, were formed representing critical tasks in the process. The GTT grouping of example tasks is based on similar task characteristics and cognitive functions. 18 Performance Influencing Factors (PIFs) could be determined and hierarchically structured. The quantification framework, consisting of 13 decision trees, was derived by identifying PIFs affecting GTTs; this included identification of 13 failure modes, 14 proximate causes and 15+ failure mechanisms. For the human failure probability estimation, a data and expert judgement based quantification of the model is used. As an application of the method, past data, FMEA, and CPT expert input will identify possible CPT failure scenarios.

PTC17-0481: Experimental Lines in Proton Therapy Centers: Specifications, solutions and Research Programs

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The pionniers protontherapy centers were installed in research facilities. The evolution since the 90′ is to install industrial turn-key hospital based facilities and, more recently, single room solutions. Some of the priorities today are (a) to have integrated solutions for clinics (including adaptive tools), (b) to increase the number of clinical protocols and (c) to reduce costs.

In parallel, there is still a wide number of research and development subjects that need to be developed that requires beam time. In some centers the treatment rooms are partially used for research (mainly off clinical hours), in others a room is devoted to research or an "end of line" is arranged to provide such a tool.

In this presentation we shall summarize the specifications and the practical implementation of experimental lines in protontherapy facilities (from single beam transport up to nearly "clinical" pencil beam lines and special proposals). The availability of dedicated rooms facilitates the set-up of complex experiments and, in different degrees, the use of the beam during clinical hours if they do not perturb the clinical work. We'll present also a comprehensive list of research subjects that are going on or proposed in those lines. They include engineering, physics, (radio)biology, and preclinical studies, but also research on applications for the space, electronics and more. We'll describe the installation of a laboratory dealing with in vivo experiments as a complex but extremely useful environment for such a facility.

PTC17-0464: Present Status of Rotating Gantry at NIRS-HIMAC

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At Heavy Ion Medical Accelerator in Chiba (HIMAC), more than 10,000 patients have been successfully treated by carbon ion beams since 1994. The successful results of treatments have led us to construct a new treatment facility equipped with a three-dimensional pencil beam scanning (PBS) irradiation system. After the construction of fixed beam lines, we started design and construction of a superconducting rotating gantry. The construction of rotating gantry was completed in September 2015. This gantry can provide the beam energy ranging from 50 to 430 MeV/u. Since the rotating gantry system requires that the beam profiles at the iso-center have no correlation between the rotation angles. We have confirmed the performance of the beam transport line with 10 gantry angles. The beam size deviation of each gantry angle are less than 10 percent of the desired value. The beam position was adjusted within 0.5 mm from mechanical isocenter for all gantry angle. We have started the commissioning of PBS system. Our PBS system is designed to treat moving target with fast rescanning as same as that of fixed beam line. In this presentation, we will report the present status of our gantry and related beam tests and initial clinical result.

PTC17-0446: Preset Status of BNCT System Using 30 MeV Cyclotron

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Sumitomo Heavy Industries (SHI) is now producing medical devices, such as PET system and Proton Therapy System, based on a-half-century history of manufacture of particle accelerators. From 2006, SHI started the development of a neutron source for BNCT based on a 30 MeV cyclotron. By collaboration with Kyoto University Research Reactor Institute (KURRI), the BNCT system was installed at KURRI campus in 2009. After the all pre-clinical tests were completed, the Phase I clinical trial was started for recurrent brain tumor in 2012. Also, the Phase I clinical trial for recurrent head and neck cancer and inoperabale case of advanced nonsquamous cell carcinoma was started in 2014. In parallel with the clinical trials, construction of same system at another site was started. The site is Southern Tohoku BNCT Research Center (STBRC) at Fukushima prefecture in Japan, and the construction was completed in 2014. From 2016, phase II clinical trials for recurrent brain tumor, recurrent head and neck cancer and inoperabale case of advanced nonsquamous cell carcinoma have been started. In 2016, another new project has been started at Osaka Medical Collage.

Overview of the projects and details of BNCT system will be presented.

PTC17-0419: Test Stand for Automatization of the Quality Assurance of the Patient Safety System in a Proton Therapy Centre

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At the Centre for Proton Therapy at the Paul Scherrer Institute cancer patients are treated in two gantries and a fixed beamline. In order to prevent non-optimal beam delivery, an interlock patient safety system (PaSS) was implemented that interrupts the treatment if any sub-system reports an error. To ensure correct treatment delivery, the PaSS needs to be thoroughly tested as part of the regular quality assurance protocols as well as after each change or upgrade. However, this testing typically required tens of man days of work, extensive beam usage and could not always cover all failure modes in the productive environment.

With the opportunity of the installation of a new gantry, an automated PaSS test stand was developed that can emulate the rest of the facility. With it we are able to test the safety system under arbitrary conditions with microsecond time resolution. It consists of a computer controlled extendable bus with configurable inputs and outputs that can be adapted to the required interface type. We have also developed a formal language to describe stimuli, expected behaviour and specific measurements. Using this automated test stand the full PaSS quality assurance procedure, including report generation, now takes 5 minutes. We present the use of our test stand in the verification and validation of the PaSS of our new gantry and demonstrate how it was used to increase safety by testing more failure scenarios than possible in the productive environment, in an automated and efficient manner.

PTC17-0217: Implementation of Efficient and Automatized Periodic Quality Assurance Procedures for Scanned Proton Beam Delivery: The MedAustron Experience

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The purpose of this work is to report on the MedAustron experience and guide medical physicists in the implementation of a complete, efficient and automatized periodic Quality Assurance (QA) of light-ion beam therapy (LIBT) delivery systems. Pencil beam system (PBS) implementation needs a follow up of the performance and specificities of the beam delivery system: Spots positions, spots sizes, depth-dose profiles and absolute dose.

The QA devices used are a 2D scintillator based detector, a multi-leaf ionization chamber detector and a parallel plate ionization chamber placed inside a water equivalent plastic phantom. They are all precisely positioned and indexed on a "hovercraft" transfer plate by dedicated holders. This QA setup stays the same for the Daily, Weekly and Monthly QA of the beam delivery system. The machine-specific QA workflow created in the OIS includes irradiation plans and predefined position of the robot couch to load the transfer plate and to position the devices precisely and reproducible to their measurement positions at the isocenter. The QA workflow can be operated from outside of the irradiation room. The analysis process is also automatized using validated in-house software for the spot and fields characterization and saved in a QA database including warnings and alarms.

The implementation of this efficient QA workflow allows a quick and extensive follow-up of the PBS beam line without any hardware compromise. QA results are reproducible, user dependency is minimized and the whole procedure can be performed within 2 hours for the daily QA with 5 energies verified.

PTC17-0097: Innovative Methods for the Characterization of Intra-Spill Beam Variations at a Slow-Extraction Synchrotron-Based Facility

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In a slow-extraction synchrotron-based facility, the intra-spill beam structure (ISBS) is tuned allowing stable beam conditions for clinical application. A typical method for the characterization of particle ranges in water is to scan an ionization chamber inside a water tank (WT). This method has associated uncertainties, mainly related to the movement of the chamber, making it unsuitable for ISBS analysis. Similarly, for transversal spot characterization commercial 2D detectors could acquire the ISBS but do not provide analysis tools enabling extraction of intra-spill variations.

The proposed ISBS analysis method is based on central spot measurements with a commercial WT, a large-area ionization chamber (LAIC) and a 2D detector system. The analysis of intra-spill range variations is based on fast acquisition of the collected charge by the LAIC in the *stationary* WT fixed at 50% of the distal Bragg Peak fall-off (dR50%). As dR50% is located in a region with a steep but quasi-*constant* dose gradient, the charge collected at dR50% is linearly correlated with the physical range at ISBS level [1]. The analysis of transversal beam variation is based on a sequence of image acquisitions made during the spill by a scintillator-CCD based detector. The in-house analysis software is able to analyze the variations of spot position and size over the spill.

The analysis method implemented improved the synchrotron acceptance process and guaranteed a beam spot and range characterization within tolerances at ISBS level. It further supported the understanding of the clinical relevance of the ISBS.

PTC17-0014: Using Field Size Factors to Characterize the In-Air Fluence of a Proton Machine with a Range Shifter

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Purpose: In this work, we present an efficient method for the commissioning of Eclipse treatment planning system (TPS) for a proton pencil beam scanning beam (PBS) system with a fixed range shifter (RS).

Materials and Methods: By combining a spiral delivery with customized control points, we were able to significantly improve measurement efficiency and obtain 250 field size factors (FSF) within three hours. The measured FSFs were used to characterize the proton fluence and fit the parameters for the double-Gaussian fluence model used in the TPS. Extensive validation was performed using FSFs measured in air and in water, absolute doses of spread-out Bragg peak (SOBP) fields, and the dose measurements carried out for patient-specific quality assurance (QA).

Results: The measured in-air FSFs agreed with the model's prediction within 3% for all 250 FSFs, and within 2% for 94% of the FSFs. The agreement between model's prediction and measurement was within 2% for the in-air and in-water FSFs and the absolute doses for SOBP beams. The patient-specific QA of 113 fields showed an excellent gamma passing rates (96.95% $\pm$2.51%) for the absolute dose comparisons with gamma criteria of 2mm and 2%.

Conclusion: The excellent agreement between the model's prediction and measurements proved the efficiency and accuracy of the proposed method of using FSFs to characterize the proton fluence and configure the TPS for a PBS system with fixed RS.

PTC17-0339: Commissioning of Helium Beams for Radiotherapy at the Heidelberg Ion Beam Therapy Facility at the University Clinic

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Heidelberg Ion Beam Therapy Facility (HIT) has treated more than 3800 patients with scanned beams of protons and Carbon ions since 2009. Currently substantial work is being done to prepare for Helium-4 irradiations at HIT. The main advantage of Helium is the significantly sharper lateral penumbra as compared to proton beams, while RBE is only moderately enhanced between entrance region and the Bragg peak. An additional Helium-4 source has been tested and installed at HIT in 2012 (1) and scanned beams of Helium ions have been provided since late 2013. Since then a complete beam library of 250 energies with different beam widths and intensities has been established. In the last years, considerable effort at HIT has been made to measure the depth dose and lateral penumbra of Helium beams and to model the nuclear fragmentation effects using the FLUKA Monte Carlo simulation code. Moreover, RBE data for clonogenic cell survival for various cell lines have been gathered in in-vitro experiments (2). These data are now used to benchmark RBE models for treatment planning. Currently the local effect model (LEM) and a data driven model (3) describing the RBE dependence on dose, LET and $(a/b)_{phtotons}$ are being investigated at HIT. For clinical treatment planning, different plannign tools are under investigation. The status of the commissioning work for Helium beams at HIT will be presented.

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Panel Discussion: Particle Therapy for Lung Cancer

PTC17-0368: Carbon-Ion Radiotherapy for T2b–4N0M0 Non-Small Cell Lung Cancer

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The safety and efficacy of carbon-ion radiotherapy for advanced non-small cell lung cancer have not been established. We evaluated the clinical outcomes of carbon-ion radiotherapy for T2b–4N0M0 non-small cell lung cancer. Twenty-three patients were treated with carbon-ion radiotherapy between May 2011 and December 2015. Seven, 14, and 2 patients had T2b, T3, and T4, respectively. The median age was 78 (range, 53–91) years, with 22 male patients. There were 12 adenocarcinomas, 8 squamous cell carcinomas, 1 non-small cell lung carcinoma, and 2 clinically diagnosed lung cancers. Eleven patients were operable, and 12 patients were inoperable. Most patients (91%) were treated with carbon-ion radiotherapy of 60.0 Gy relative biological effectiveness (RBE) in 4 fractions or 64.0 Gy (RBE) in 16 fractions. Local control and overall survival rates were calculated. The median follow-up of surviving patients was 25 months. Three patients experienced local recurrence, and the 2-year local control rate was 81%. During follow-up, 5 patients died of lung cancer, and 1 died of intercurrent disease. The 2-year overall survival rate was 70%. Operable patients had a better overall survival rate compared with inoperable patients (100% *vs.* 43%; $P = 0.04$). There was no grade $\geq$2 radiation pneumonitis. Carbon-ion radiotherapy was effectively performed for T2b–4N0M0 non-small cell lung cancer without severe adverse events. A Japanese multi-institutional study is ongoing to prospectively evaluate these patients and establish the use of carbon-ion radiotherapy.

PTC17-0096: Carbon-Ion Radiotherapy for Lung Cancer Patients with Interstitial Lung Disease

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Purpose: Lung cancer is frequently complicated by interstitial lung disease (ILD). Treatments protocols for ILD-lung cancer patients have not been established as surgery, chemotherapy, and radiotherapy can all cause acute exacerbation of ILD. In this study we evaluated the toxicity and efficacy of carbon ion radiotherapy (CIRT) in patients with lung cancer (LC) with ILD.

Materials and Methods: Between June 2004 to August 2016, 40 patients who were diagnosed with LC and ILD were treated with CIRT. Owing to prior symptomology, radiation pneumonitis (RP) and symptom progression pre- and post-treatment were evaluated. 22 patients had symptoms such as dyspnea or hypoxia (O_2 indicated) before the CIRT. The relationships between RP and clinical factors were investigated.

Results: There were 40 patients (37 male, 3 female), ranging from 62-90 years old. The median follow-up period was 22.6 months. Single-grade symptomatic progression (e.g., grade 2 to grade 3) was seen in 5 patients, and a two-grade increase was seen in 1 patient. Two patients with Grade 3 RP experienced radiation-induced acute exacerbation of ILD. RP post-treatment progression correlated with dosimetric factors (V5, V10, V15, and V20).

Conclusion: Carbon ion radiotherapy can be used as a low risk, curative treatment for LC patients with ILD as it is a minimally invasive procedure and has excellent dose localization. The result of this study suggested the importance of minimizing low dose region so as to reduce a risk of severe RP.

PTC17-0044: Consensus Guidelines for Implementing Pencil Beam Scanning Proton Therapy for Thoracic Malignancies on Behalf of PTCOG Thoracic and Lymphoma Subcommittee

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Pencil beam scanning (PBS) proton therapy (PT), particularly intensity-modulated proton therapy, represents the latest advanced proton therapy technology for treating cancers, including thoracic malignancies. PBS proton therapy has enormous potential in its ability to tightly tailor the dose to the target while sparing critical structures, thereby reducing treatment-related toxicities, particularly for tumors in areas with complicated anatomy. However, implementing PBS-PT for moving targets has several additional technical challenges compared with intensity-modulated photon radiotherapy or passive scattering proton therapy. Four-dimensional computerized tomography–based motion management, robust optimization and evaluation are crucial for minimizing uncertainties associated with beam range and organ motion. Rigorous quality assurance is required to validate dose delivery both before and during the course of treatment. Active motion management (e.g., breath hold), beam gating, rescanning, tracking or adaptive planning may be needed for cases involving significant motion or changes in motion or anatomy over the course of treatment. Preliminary results have shown that PBS-PT technology can be safely implemented in the treatment of thoracic cancers with minimal motion, and clinical outcomes seem promising. As additional proton centers, many exclusively with PBS technology, are being built around the world, the need for guidelines and consensus to address these issues associated with PBS-PT is increasingly desirable. To meet this need, the Particle Therapy Co-Operative Group (PTCOG) Thoracic/Lymphoma Subcommittee developed this consensus guideline, based on available physics and clinical findings, for the use of PBS-PT including IMPT for thoracic tumors.

PTC17-0546: Particle Therapy for Lung Cancer – Is It as Effective as Surgery?

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Surgery and radiotherapy are both considered to be local therapy. Surgery is curative when all cancer cells are removed with the specimen regardless the viability of the cancer cells. Radiotherapy is curative when all cancer cells are existing within the irradiated area and they are all necrosed. We have reported VATS lobectomy offers significantly more favorable long-term outcomes than SBRT in potentially operable patients with biopsy proven clinical stage I NSCLC. We have also reported that SBRT can be an alternative treatment option to sublobar resection patients who cannot tolerate lobectomy because of medical comorbidities. Particle therapy has been reported to be a promising modality for medically inoperable patients with localized NSCLC due to narrow dose localization leading to concentrated irradiation while sparing the surrounding healthy tissue. However, direct comparisons between particle therapy and the best available photon treatment, such as SBRT, have never been reported. Therefore, the clinical efficacy of particle therapy remains unclear, resulting also in unproven cost-effectiveness. Successful salvage resection for local recurrence after carbon ion radiotherapy has been reported. More evidence is required before particle therapy can be used as an alternative treatment to surgery for lobectomy tolerable patients with stage I NSCLC.

PTC17-0545: How Can We Cure the Lung Cancer Patients?

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Until now, only surgical resection and radiation therapy are the only way to cure the patients with lung cancer. Therefore, limited disease is the critical limit to cure. Recently, precision medicine and immunological therapy has gained dramatic survival over previous traditional chemotherapy to the subset of patients. Most effective targeted therapy, alectinib to patients with ALK gene translocation, can obtain survival for more than 3 years. Anti-PD-1 inhibitor are also dramatically effective, if only no more than 20% can enjoy the benefit and enriching those patients is still extremely difficult. There are some patients who are as if cured, that is in complete remission since the start of phase I study. We are now facing the time to thinking about how to evaluate efficacy of treatment if they can cure the patients. Is the treatment having a 1-year survival rate of 50% and 5-year survival rate of 1% better than the treatment having a 1-year survival rate of 10% and 5-year survival rate of 10%? In this lecture, I will summarize the recent data of medical oncology, and discuss the evaluation method of treatment with potentially curability of cancer.